From DEPARTMENT OF MOLECULAR MEDICINE AND SURGERY
Karolinska Institutet, Stockholm, Sweden

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) FOR THE TREATMENT OF CARDIOGENIC SHOCK: IDENTIFICATION OF PRE-IMPLANT OUTCOME PREDICTORS

Thomas Fux

Karolinska Institutet

Stockholm 2018

Published by Karolinska Institutet.

ISBN 978-91-7831-190-3
Printed by Eprint AB 2018

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) FOR THE TREATMENT OF CARDIOGENIC SHOCK: IDENTIFICATION OF PRE-IMPLANT OUTCOME PREDICTORS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Thomas Fux, M.D.

Principal Supervisor:
Professor Jan van der Linden
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Cardiothoracic Anesthesiology and Intensive Care

Co-supervisor(s):
Professor Lars H. Lund
Karolinska Institutet
Department of Medicine
Division of Cardiology

Associate Professor Matthias Corbascio
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Cardiothoracic Surgery

Opponent:
Associate Professor Göran Dellgren
University of Gothenburg
Department of Molecular and Clinical Medicine
Institute of Medicine
Division of Cardiothoracic Surgery

Examination Board:
Associate Professor Jan Hultman
Uppsala University
Department of Surgical Sciences
Division of Anesthesiology and Intensive Care

Associate Professor Jan Anders Ahlsson
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Cardiothoracic Surgery

Associate Professor Laila Johansson Hellgren
Uppsala University
Department of Surgical Sciences
Division of Cardiothoracic Surgery

“Minds are like parachutes — they function only when they are open.”

Thomas Dewar

ABSTRACT

Background: Refractory cardiogenic shock (RCS), cardiac arrest (CA) and postarrest cardiogenic shock (CS) are associated with high mortality. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly used and can offer acute cardiopulmonary life support in this critically ill population but selection of VA-ECMO candidates remains challenging. There are limited data on which pre-VA-ECMO variables that predict outcome.

Aims: To identify pre-VA-ECMO predictors for 90-day mortality in **Study I** unselected, **Study II** postcardiotomy and **Study III** non-surgical patients with RCS, and **Study IV** in patients with CA or postarrest cardiogenic shock prior to VA-ECMO were studied.

Methods: Study I-IV were observational and retrospective. **Study I** included 181 mixed patients with RCS, **Study II** 105 patients with refractory postcardiotomy CS, **Study III** 76 non-surgical patients with RCS and **Study IV** 72 patients with CA or postarrest CS prior to VA-ECMO cannulation. The association between pre-implant variables and all-cause mortality at 90 days was analyzed with uni- and multivariable logistic regression.

Results: Study I. Main etiologies of RCS were post-cardiotomy failure 58%, acute myocardial infarction 22% and other medical etiologies 20%. Median duration of VA-ECMO support was 7 days (interquartile range [IQR]: 3-13). The 90-day overall mortality was 54%. Arterial lactate (odds ratio [OR] per unit: 1.14; 95% confidence interval [CI]: 1.06-1.23; p <0.001), number of inotropes and vasopressors (OR per agent: 1.58; 95% CI: 1.13-2.21; p = 0.008), and ischemic heart disease (IHD), (OR: 2.90; 95% CI: 1.31-6.39; p = 0.008) were independent predictors of 90-day mortality. **Study II.** Main surgical subgroups were single non-CABG 29%, isolated CABG 20%, 2 and 3 concomitant surgical procedures, 31% and 20%, respectively. Median duration of VA-ECMO was 7 days (IQR: 3-14). The 90-day overall mortality and in-hospital mortality was 57% and 56%, respectively. Arterial lactate (OR per unit: 1.22; 95% CI:1.07-1.40; p = 0.004), and IHD (OR: 7.87; 95% CI: 2.55-24.3; p <0.001) were independent predictors of 90-day mortality. **Study III.** Main etiologies of RCS were acute myocardial infarction 51% and acute heart failure of other etiologies 49%. Median duration of VA-ECMO was 5 days (IQR: 2-11). The 90-day overall mortality was 49% and in-hospital mortality was 50%. Arterial lactate (OR per mmol/L: 1.15; 95% CI: 1.06-1.24; p = 0.001) and number of inotropes and vasopressors (OR per agent: 2.14; 95% CI: 1.26-3.63; p = 0.005) were independent predictors of 90-day mortality. **Study IV.** Out-of-hospital CA occurred in 12% of the patients. Initial cardiac rhythm was non-shockable in 57%, and shockable in 43% of the patients. Median cardiopulmonary resuscitation duration was 21 minutes (IQR: 10-73, range:1-197). No return of spontaneous circulation (ROSC) was present in 64% and postarrest CS in 36% of the patients at VA-ECMO cannulation. Median duration of VA-ECMO was 5 days (IQR: 2-12). The 90-day overall mortality and in-hospital mortality were 57%, respectively, and 53% died during VA-ECMO. All survivors (43%) had cerebral performance category score 1-2 at discharge to home. Initial non-shockable CA rhythm (OR: 12.2; 95% CI 2.83-52.7; p = 0.001), arterial lactate (OR per unit: 1.15; 95% CI: 1.01-1.31; p = 0.041), and IHD (OR: 7.39; 95% CI: 1.57-34.7; p = 0.011) as independent predictors of 90-day mortality.

Conclusions: Identified independent pre-implant predictors for 90-day mortality after VA-ECMO initiation were in **Study I** arterial lactate, number of inotropes and vasopressors, and IHD, **Study II** arterial lactate and IHD, **Study III** arterial lactate, number of inotropes and vasopressors, **Study IV** initial non-shockable CA rhythm, arterial lactate and IHD. These predictors are easily available for pre-VA-ECMO risk prediction.

LIST OF SCIENTIFIC PAPERS

I. **Fux T**, Holm M, Corbascio M, van der Linden J, Lund LH.
Pre-Implant Outcome Predictors in Patients with Refractory Cardiogenic Shock supported with VA-ECMO.
J Am Coll Cardiol 2017 Oct 17;70(16):2094-2096

II. **Fux T**, Holm M, Corbascio M, Lund LH, van der Linden J.
Venoarterial Extracorporeal Membrane Oxygenation for Postcardiotomy Shock: Risk Factors for Mortality.
J Thorac Cardiovasc Surg 2018 (In press)

III. **Fux T**, Holm M, Corbascio M, Lund LH, van der Linden J.
VA-ECMO Support in Non-Surgical Patients with Refractory Cardiogenic Shock: Pre-Implant Outcome Predictors.
Artificial Organs 2018 (In press)

IV. **Fux T**, Holm M, Corbascio M, van der Linden J.
Cardiac Arrest Prior to Venoarterial Extracorporeal Membrane Oxygenation; Risk Factors for Mortality.
Submitted

CONTENTS

LIST OF ABBREVIATIONS

AHF	acute heart failure
AMI	acute myocardial infarction
CABG	coronary artery bypass grafting
CI	cardiac index
CO	cardiac output
CPB	cardiopulmonary bypass
CPC	cerebral performace category
CPR	cardiopulmonary resuscitation
ECPR	extracorporeal cardiopulmonary resuscitation
euroSCORE	European System for Cardiac Operative Risk Evaluation
IHD	ischemic heart disease
LVEF	left ventricular ejection fraction
PCI	percutaneous coronary intervention
ROSC	return of spontaneous circulation
VA-ECMO	venoarterial extracorporeal membrane oxygenation

1 INTRODUCTION AND BACKGROUND

Cardiogenic shock occurs in 7-10% of patients with acute myocardial infarction (AMI),[1] in 1% of patients following cardiac surgery[2] and additionally affects patients with decompensated heart failure of other etiologies.[3] The in-hospital mortality rate of cardiogenic shock varies between 40% and 90% depending on etiology, patient characteristics and therapeutic interventions.[1, 3] Refractory cardiogenic shock, defined as cardiogenic shock unresponsive to conventional medical therapy, will unavoidably proceed to death.[4] Refractory cardiogenic shock still has an overall in-hospital mortality rate of around 50%,[3, 5] despite initiation of mechanical circulatory support systems.

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is designed to temporarily (days to weeks) provide partial or complete (biventricular) cardiac or cardiopulmonary (in cases with concomitant pulmonary failure) support in patients with refractory cardiogenic shock, regardless of cause, aiming to bridge-to-decision, bridge-to-recovery i.e. the failing heart to functional recovery, or bridge-to-destination i.e. heart transplantation, long-term mechanical circulatory support, or other interventions including percutaneous coronary intervention (PCI) and cardiac surgery.[6, 7]

The VA-ECMO circuit, implantation technique, and patient management during VA-ECMO is not the focus of this thesis and have been described in detail elsewhere.[5, 6, 8-10] In short, the standard VA-ECMO procedure included whenever feasible cannulation of the femoral artery and vein or right internal jugular vein, typically using the Seldinger technique, by an open (surgical cut down) or percutaneous approach, along with an ipsilateral distal perfusion catheter to prevent limb ischemia.[11] Central cannulation of the right atrium and ascending aorta is occasionally performed on patients who cannot be weaned from cardiopulmonary bypass (CPB) or because of lack of suitable peripheral vascular access.

The VA-ECMO-circuit used in this thesis consisted of an external centrifugal pump (CardioHelp-i, Maquet, Rastatt, Germany or Thoratec CentriMag system, Pleasonton, CA, USA), a membrane oxygenator (Maquet HLS Module Advanced) and a tubing system (Maquet Bioline) with an integrated heat exchanger that ensure both circulation and oxygenation of tissues. The system has integrated pressure sensors, a venous probe to measure venous oxygen saturation, hemoglobin, hematocrit, venous temperature, and a flow-bubble sensor. Deoxygenated blood is drained from the venous system and is pumped through a membrane oxygenator (artificial lung) before returning as oxygenated blood to the patient´s arterial circulation, in a similar fashion to standard CPB, which in contrast usually

includes a cardiotomy reservoir. By facilitating oxygen and carbon dioxide exchange, ECMO allows for reduction of ventilator settings (lung protective ventilation) or complete stop of ventilation to diminish the potential for lung injury.[12] The major difference between the two main ECMO configurations, VA- and veno-venous (VV)-ECMO circuits (besides the veno-pulmonary artery [VPa], veno-veno-arterial [VVA], veno-arterial-veno [VAV] and veno-arterial-pulmonary artery [VAPa] modes) (**Table 1**) is the vascular insert location for the supply and drainage cannulas.[13] The latter is only initiated in patients with isolated respiratory failure to provide pulmonary support while the lungs recover. This is achieved by draining deoxygenated blood from either the inferior vena cava by the femoral vein and returned to the right internal jugular vein, or vice versa (the latter not included in the original reference for **Table 1**), or by applying a bicaval dual-lumen catheter to provide both drainage and return directly into the right atrium via the internal jugular vein, without the need to insert a second venous cannula.

TABLE 1. Cannulation modes for peripheral extracorporeal membrane oxygenation (ECMO)

Drainage		Return		Strategy	Draining cannula*	Supplying cannula*	Indication
	V	V		VV	Inferior vena cava or superior vena cava†	Superior vena cava or inferior vena cava†	ARDS
	V	Pa		VPa	Right atrium	Pulmonary artery	Rightsided cardiogenic shock
	V	A		VA	Right atrium or superior vena cava†	Common iliac artery	Postcardiotomy cardiogenic shock Cardiogenic shock of other etiology Massive pulmonary embolism High risk PCI support Extracorporeal resuscitation
V	V	A		VVA	Inferior vena cava Superior vena cava	Common iliac artery	Insufficient unloading during VA-ECMO Left ventricular distension during VA-ECMO
	V	A	V	VAV	Inferior vena cava	Common iliac artery Superior vena cava	Respiratory failure during VA-ECMO Cardiogenic shock during VV-ECMO
	V	A	Pa	VAPa	Right atrium	Common iliac artery Pulmonary artery	Severe rightsided heart failure during VAV-ECMO Severe lung and rightsided heart failure during VA-ECMO

A, arterial; *ARDS*, acute respiratory distress syndrome; *Pa*, pulmonary artery; *PCI*, percutaneous coronary intervention; *V*, venous. The nomenclature does not consider the arterial cannula for distal leg perfusion and does not change upon use of a bicaval dual-lumen cannula (VV-ECMO). *Typical place of blood supply/drainage (cannula tip), not place of vascular access/puncture. †Not included in the original table reference by L. Napp and J. Bauersachs.

VA-ECMO support has been reported to improve short and long-term survival in refractory cardiogenic shock in large registries, but with divergent success depending on etiology, patient characteristics and interventions.[7, 14, 15] Furthermore, VA-ECMO is much less expensive than comparable mechanical circulatory support alternatives and can be rapidly deployed (within 15 minutes) by percutaneous insertion without access to the operating room.

The concept of ECMO was first described in the 1970s.[16, 17] Despite major advances in technology since it was first developed, VA-ECMO remains invasive, resource demanding, and associated with considerable risk for severe complications.[6, 18-22] These include life-threatening gas embolism, massive hemorrhage secondary to tubing ruptures or disconnections, blood clots in the circuit, loss of circuit flow (usually secondary to hypovolemia or suboptimal cannula placement), left ventricular distension as a consequence of the VA-ECMO initiated retrograde aortic flow, which causes a marked increase in the left ventricular afterload, impairing myocardial performance especially in severe contractile dysfunction,[10, 23] differential hypoxia ("two circulation-syndrome"),[24-27] thromboembolic events, infections, limb ischemia or secondary consequences of prolonged immobilization, and primary failure of circuit components. The potential life-saving benefits of VA-ECMO must therefore be weighed against its inherent risks and should therefore be restricted to selected patients in a medically appropriate and resource efficient manner.

Data on prognosis and prognosing factors in patients treated with VA-ECMO are scarce and limited by small to moderate sample sizes and/or relatively short duration of follow-up.[28-35] Although evidence is lacking, VA-ECMO use in patients with refractory cardiogenic shock or cardiac arrest has risen considerably in recent years.[36-38] Optimal selection of patients with refractory cardiogenic shock for VA-ECMO support is a field of increased interest due to promising outcomes in critically ill patients.[14, 39-43]

The majority of studies have focused on postcardiotomy shock patients,[2, 8, 34, 44-47] were VA-ECMO is initiated in 0.6-2.9% of patients after routine cardiothoracic surgery.[2, 34, 44, 46-50] The postcardiotomy cardiogenic shock VA-ECMO studies have focused on a combination of preoperative, surgical, and on-VA-ECMO (i.e. during support) variables to identify outcome predictors.[8, 34, 44, 46, 47, 49-51] Despite VA-ECMO support, the in-hospital mortality rate in postcardiotomy cardiogenic shock is 53-84%[50, 52-56] and is influenced by patient characteristics and surgical case mix.[2, 34, 57]

Residual studies have evaluated non-surgical subgroups[40, 58-62] or a combination of non-surgical and surgical populations,[14, 35, 39, 53, 63, 64] which makes the interpretation more difficult

as the two cohorts have different pathophysiological mechanisms. Limited data on independent pre-VA-ECMO outcome predictors in an unselected non-surgical population with refractory cardiogenic shock have been identified as previous studies have mainly included variables in the analysis from both before and after VA-ECMO was initiated.[65, 66] Furthermore, previous studies have usually omitted to report rates of missing data or have presented results with considerably incomplete data[14, 32, 33, 40, 61, 66] In addition, it is problematic to include variables after VA-ECMO initiation (i.e. during support) when the specific aim is to determine which patients who should be selected to receive this highly invasive therapy. Although refractory cardiogenic shock represents the majority of adult patients on VA-ECMO,[15] studies exclusively focusing on independent pre-VA-ECMO factors to facilitate pre-implant risk prediction of midterm outcomes in different refractory cardiogenic shock population have only scarcely been described.

There are important medical, ethical and resource utilization aspects which motivate this thesis. VA-ECMO has the potential to save many lives but has heavy up-front costs and is associated with potentially severe complications. As this field expands it is important that selection criteria and ultimately guidelines are established. If VA-ECMO continues to be utilized based on vague and varying clinical indication, it is likely that payers will severely restrict its application and the potential to help many patients will be foregone.[6]

Three main goals for VA-ECMO risk prediction can be considered. First, it should allow clinicians to prospectively stratify the outcome risk for VA-ECMO candidates. Second, it should also permit clinicians to retrospectively understand their risk-adjusted VA-ECMO performance across all their patients. Third, it should allow clinicians who wish to start an ECMO program to estimate future clinical performance from such a program.[38] Hence, appropriate patient selection, timing for VA-ECMO initiation and identification of pre-VA-ECMO predictors for survival are vital.[64, 67]

The overall ambition of this thesis was to identify specifically pre-implant predictors for short and mid-term outcome in patients with cardiogenic shock of different etiologies supported with VA-ECMO. A further ambition was to present outcome data in predefined subgroups of patients, which may contribute to improve identification of suitable candidates before implant, increase our ability to predict outcome and handle patients during VA-ECMO.

2 AIMS

The specific aims were:

- To identify independent pre-VA-ECMO predictors for 90-day mortality in an undifferentiated refractory cardiogenic shock population supported by VA-ECMO.

- To identify independent pre–VA-ECMO predictors for 90-day mortality in an unselected population with refractory postcardiotomy cardiogenic shock supported by VA-ECMO.

- To identify independent pre-VA-ECMO predictors for 90-day mortality in an unselected non-surgical population with refractory cardiogenic shock.

- To identify independent pre-VA-ECMO predictors for 90-day mortality in patients with cardiac arrest and CPR ≥1 minute prior to VA-ECMO, independently if VA-ECMO was initiated during CPR or if ROSC was achieved but postarrest cardiogenic shock ensued.

3 METHODS

3.1 STUDY DESIGN AND PATIENT SELECTION

Study I-IV were observational, retrospective, single tertiary center studies where we in **Study I** started by reviewing the medical records of 181 consecutive patients, who received VA-ECMO support for refractory cardiogenic shock between September 2006 and April 2015 at the Department of Cardiothoracic Surgery and Anesthesiology at the Karolinska University Hospital in Stockholm, Sweden. VA-ECMO was initiated due to refractory cardiogenic shock as a rescue therapy when other therapeutic options were exhausted.

In **Study II** we restricted the inclusion criteria to patients who received VA-ECMO support for refractory postcardiotomy cardiogenic shock during the same study period resulting in 105 consecutive patients. The patients were included in the study irrespective of locality or timing of VA-ECMO initiation, i.e. intraoperatively or postoperatively in the ICU.

The 76 consecutive patients with refractory cardiogenic shock included in **Study III** had not undergone surgery prior to VA-ECMO implantation.

The selection criteria for **Study IV** were 72 patients presenting with in- or out-of-hospital cardiac arrest, presumed or confirmed to be of cardiac etiology by presenting symptom, coronary angiography, echocardiography, and computed tomography where applicable, receiving conventional CPR duration (low-flow duration) of $\geq$1 minute and where CPR either continued until VA-ECMO had been employed or resulted in sustained return or spontaneous circulation (ROSC) followed by refractory postarrest cardiogenic shock before VA-ECMO. All cardiac arrests were witnessed by trained medical personnel who immediately initiated conventional CPR (emergency medical team present at start of out-of-hospital cardiac arrest), which limited the no-flow time to almost zero and excluded by-stander impact on CPR quality. Patients with out-of-hospital cardiac arrest were transported to our institution for immediate evaluation for suitability as candidates for VA-ECMO support (all cannulations were performed in-hospital).

3.2 CLINICAL INTERVENTIONS AND PROCEDURES

At present, there are no universal criteria for initiation of VA-ECMO support for refractory cardiogenic shock. Our unit considers VA-ECMO as salvage therapy for evidence of persistent hypoperfusion and tissue hypoxia, secondary to severe and refractory cardiac or cardiopulmonary failure, despite adequate intravascular volume loading and support with high doses of inotropes and vasopressors.

Patients were candidates for VA-ECMO support when there was a potential for recovery, heart transplantation or as a bridge to long-term mechanical assist device (LVAD). Exclusion criteria included cerebral hemorrhage, severe aortic valve insufficiency, aortic dissection, short-life expectancy due to other medical conditions, advanced age, or non-witnessed cardiac arrest. All patients were considered to have negligible chance of survival without initiating VA-ECMO support. The final decision for initiation of VA-ECMO was made by the cardiothoracic surgeon, the cardiothoracic intensivist, and the ECMO specialist. The device, implantation technique and patient management has been described elsewhere.[5, 6, 8, 9, 42] In brief, the standard VA-ECMO procedure included whenever feasible cannulation of the femoral artery and vein either by surgical cut down or percutaneous puncture, along with a distal perfusion catheter to prevent limb ischemia (**Figure 1**).

Central cannulation of the right atrium and ascending aorta was occasionally performed on patients who could not be weaned from cardio-pulmonary bypass (CPB) or because of lack of suitable peripheral vascular access. The VA-circuit consisted of a centrifugal pump (CardioHelp-i, Maquet, Rastatt, Germany or Thoratec CentriMag system, Pleasonton, CA, USA), a membrane oxygenator (Maquet HLS Module Advanced) and a tubing system (Maquet Bioline) with an integrated heat exchanger. Suitable refractory cardiogenic shock patients at external hospitals were placed on VA-ECMO and transported to our institution by our mobile ECMO unit.

In general, when cardiac and pulmonary recovery was considered to be adequate weaning from VA-ECMO was attempted. If weaning failed and no further cardiac recovery was expected, bridging to LVAD or transplantation was considered as an alternative in patients with a suspected favorable neurological prognosis. Patients with severe neurological injuries were weaned off VA-ECMO during withdrawal of life support.

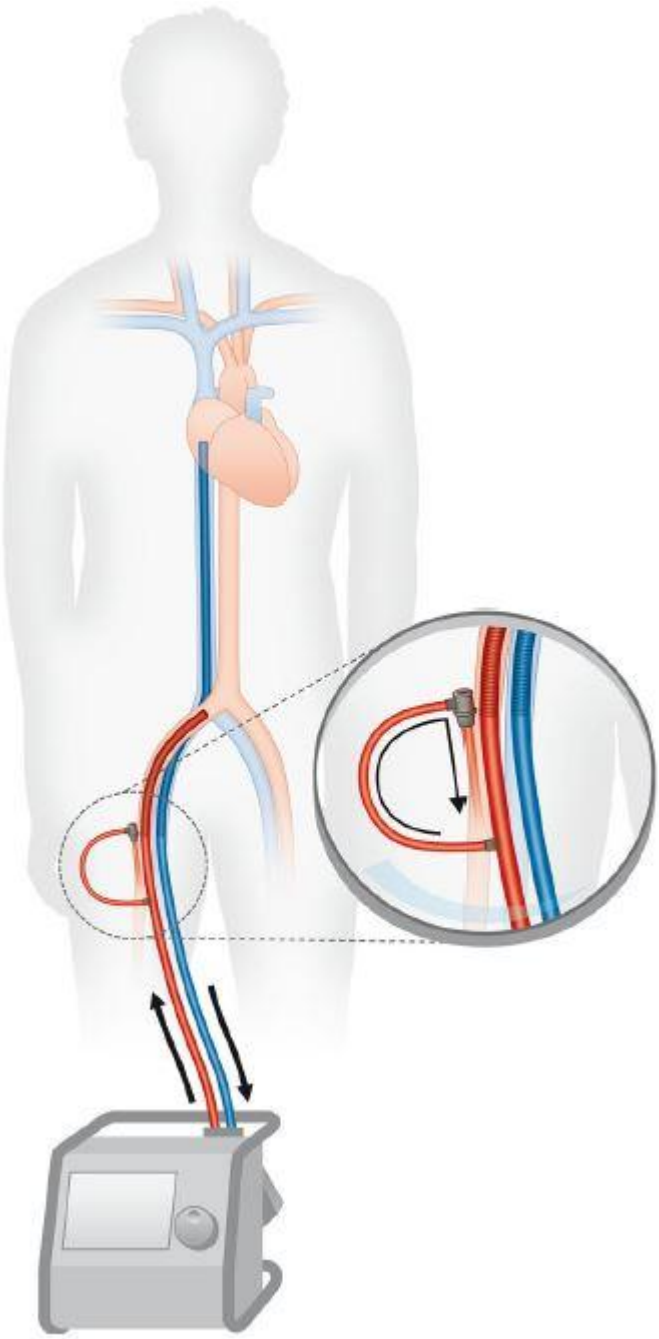

FIGURE 1. Venoarterial (VA)-ECMO via the femoral vessels drains venous blood (blue) from the right atrium and returns an equal volume after reoxygenation and decarboxylation (red) to the iliac artery towards the aorta. Femoral artery cannulation requires an extra shunt cannula for antegrade perfusion of the leg (inset).

Regarding weaning from CPB in surgical patients, no registration of the number of weaning attempts was documented to allow complete inclusion and evaluation. But more importantly, there is no general protocol for the individual weaning procedure from CPB. The weaning procedure is individualized primarily depending on the individual patient's cardiovascular response to the lowering of the CPB flow rate but also on the preferences of the individual surgeon and intensivist. In uncomplicated cases where patients display a sufficient cardiac reserve the weaning procedure can be performed more rapidly during simultaneous

assessment of cardiac function (including evaluation of the preceding surgical procedure performed e.g. valve repair, coronary graft flow etc.). In other cases, remaining valve issues or insufficient coronary anastomotic flow etc. may become overt during low CPB weaning flow rates with need for additional valve or coronary anastomotic re-interventions whereby the weaning procedure is aborted and full CPB is reinstituted. If the surgical reintervention is successful these patients may be weaned at the second attempt but will in case with focus on numbers of weaning attempts be registered as having undergone two weaning attempts which could be interpreted as more "worse" than patients that fail the first weaning attempt due to surgically non-restorable refractory postcardiotomy shock and not a more "benign" and correctable surgical cause. The pre-VA-ECMO cardiovascular state in patients with refractory postcardiotomy shock can be considered to contain more robust data when to identify pre-VA-ECMO outcome predictors compared with the more subjectively decided number of weaning attempts or other pre-VA-ECMO interventions.

3.3 DATA COLLECTION

Patient's characteristics, complications and outcome data were acquired from medical records, including clinical presentation, interventions and the latest available laboratory data before VA-ECMO onset, and were retrospectively analyzed. Patients were in **Study I-IV** divided between survivors and non-survivors at 90 days after VA-ECMO-initiation. Additionally, in each study patients were further subdivided in mutually exclusive groups; **Study I:** AMI, postcardiotomy and other medical etiologies; **Study II:** single non-coronary artery bypass grafting (non-CABG), isolated CABG, and 2 and 3 concomitant surgical procedures according to the euroSCORE II classification (European System for Cardiac Operative Risk Evaluation) of cardiac surgical procedures; **Study III:** AMI and acute heart failure (AHF) of other etiologies, and **Study IV:** Absence of ROSC and postarrest cardiogenic shock i.e. ROSC.

3.4 ETHICS

The thesis is based on four retrospective studies, all patients had already received VA-ECMO support as they were considered to have negligible chance of survival without initiating VA-ECMO support. Therefore, no randomization was performed between receiving VA-ECMO support or to proceed with pharmacological, volume loading or support with other mechanical support systems (i.e. intra-aortic balloon pump [IABP], Impella®, TandemHeart™). Such a

randomization would have raised serious ethical concerns in this population being under acute life-threatening conditions.

This thesis will contribute to a better identification of suitable candidates before implant and increase our ability in prognosing and treating patients on VA-ECMO.

The studies of this thesis conform to the principles of the Helsinki Declaration and ethics approval has been obtained from the Regional Ethical Review Board in Stockholm (Project No. 2008/1695-31, 2012/119-32). No individual patient or family consent was obtained. No experimental interventions were performed.

3.5 DEFINITIONS

The definitions used throughout the thesis conform to those presented in **Study I-IV** to avoid any misinterpretation. Refractory cardiogenic shock was defined as cardiogenic shock with evidence of progressive tissue hypoxia and end organ failure unresponsive to conventional medical therapy including inotropes and adequate fluid management. Ischemic heart disease (IHD) was defined as a history of myocardial infarction, angina pectoris, percutaneous coronary intervention/CABG, or when prior coronary angiography had shown evidence of coronary artery disease according to multidisciplinary conferences. Chronic renal failure was defined as the estimated preoperative glomerular filtration rate of less than 60 mL/min/1.73 m2 present for more than 3 months (in accordance with the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines 2012).[68] Number of inotropes and vasopressors was defined as the total number of intravenous inotropes and vasopressors (epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan), pre-VA-ECMO data as the latest clinical and laboratory data just before VA-ECMO cannulation, and data defined "prior" refers to data previous to the current medical event/admission. Chronic cardiomyopathy was defined as symptomatic, non-ischemic or ischemic cardiomyopathy for more than 6 months since diagnose or if a second hospitalization due to heart failure decompensation occurred within 6 months from diagnosis. Multiorgan failure was defined as physiological derangement in 2 or more organ systems.

CPR included all cardiopulmonary resuscitation episodes from the time of the current hospital admission: preoperative (before CPB) and postoperative until initiation of VA-ECMO (**Study II**). CPR included all CPR episodes within 12 hours before VA-ECMO onset

(**Study I, III-IV**). No-flow duration was defined as the time (without chest compressions) from cardiac arrest to initiation of CPR, and low-flow duration as the time with CPR (i.e. CPR duration) until sustained ROSC was achieved or VA-ECMO initiated. ROSC was defined as the restoration of a spontaneous perfusing rhythm (evidence of restored circulation) that resulted in breathing (more than an occasional gasp), palpable pulse, measurable blood pressure or an arterial waveform (approximately >30 seconds), with no chest compressions given. Postarrest cardiogenic shock following sustained ROSC was defined as myocardial dysfunction with progressive hypoperfusion and tissue hypoxia refractory to intravascular volume loading and increasing doses of inotropic and vasopressor agents.

3.6 OUTCOME DEFINITIONS

3.6.1 Primary outcome

The primary outcome was defined as death from any cause at 90 days after VA-ECMO cannula insertion (**Study I-IV**).

3.6.2 Secondary outcomes

Successful weaning was defined as survival more than 48 hours after weaning from VA-ECMO or without need of re-initiation of VA-ECMO. Favorable neurological outcome was defined as cerebral performance category scores[69] of 1 (good performance) and 2 (moderate disability) on a 5-point scale (**Table 2**) at the time of hospital discharge to home (**Study II-IV**).

TABLE 2. Cerebral performance category score

CPC score	Cerebral Performance
CPC 1	Good cerebral performance: conscious, alert, able to work, might have mild neurological or psychological deficit
CPC 2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment
CPC 3	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
CPC 4	Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
CPC 5	Brain death: apnea, areflexia, EEG silence, etc.

CPC, cerebral performance score*; EEG,* electroencephalogram

3.7 STATISTICS

The statistical methods used in the **Study I-IV** were coherent as the overall aim of the thesis was to identify preimplant outcome predictors. No patients were lost to follow up in **Study I-IV**.

Initial analysis compared pre-VA-ECMO variables between survivors and non-survivors at 90 days after initiation of VA-ECMO support. Categorical variables were presented as numbers and percentages, and compared with the Chi-square, Likelihood ratio or Fisher's exact tests. Whereas most continuous baseline variables were non-normally distributed, a conservative approach was taken with all data expressed as median and interquartile range (IQR) and compared with the Mann-Whitney *U* test. A univariable logistic analysis was used to determine the pre-VA-ECMO-implant variables for death at 90-days after VA-ECMO initiation. Statistical significance was set to $p < 0.05$. Prior to multivariable logistic regression analysis, variables identified as being significant in the univariable analysis were subjected to multicollinearity analysis by using the Spearman rho correlation coefficient.

To assess the impact of non-linearity on the logistic regression analysis (**Study II-IV**) the continuous variables included in the model were tested by using restricted cubic splines with both 3 and 4 knots (default placements). Inclusion of restricted cubic splines in the statistical analysis provides a method to formally test the assumption of a linear relationship between a predictor and the outcome using standard methods i.e. testing the hypothesis that the relationship is not linear or summarizing a relationship that is too non-linear to be usefully summarized by a linear relationship. Failure to identify nonlinearity and include it in a model can result in an overestimated or underestimated relationship, or a relationship that is missed altogether. When non-linear relationships exist, splines allow it to be modelled well, reducing model misspecification and providing insight into the relationship between predictor and outcome (Croxford. R. Restricted Cubic Spline Regression: A Brief Introduction. Paper 5621-2016. Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada, http://support.sas.com/resources/papers/proceedings16/5621-2016.pdf). The acquired Akaike information criterion (AIC) and Bayesian information criterion (BIC) values were then compared with the corresponding AIC and BIC values of the original models.

Goodness of fit was verified by the Hosmer-Lemeshow´s test indicating that the number of deaths was not significantly different from those predicted by the models and that the overall

fit of the models was good. A cumulative survival curve for 90 days follow-up was generated utilizing the Kaplan-Meier method and compared using the log rank test. Statistical analyses were performed with SPSS version 23 and 25 for Windows (IBM SPSS Statistics, NY, US) and Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX, US).

4 RESULTS

No patients were lost to follow up and there were no VA-ECMO device-related deaths in **Study I-IV**.

4.1 STUDY I

Pre-VA-ECMO variables and comparison between survivors and non-survivors within 90 days after initiation of VA-ECMO support are summarized in **Table 3**. Median age was 58 years (interquartile range [IQR]: 47-66), which was significantly lower in survivors (55 years; IQR: 40-64) compared with non-survivors (61 years; IQR: 50-67; p = 0.007). Overall, the most common (mutually exclusive) indication for VA-ECMO support was postcardiotomy (n = 105; 58%), followed by AMI (n = 39; 22%) and other medical etiologies (n = 37; 20%). IHD was present in 56% (n = 102) of the study population, and the corresponding values for multiorgan failure, arterial lactate, number of inotropes and vasopressors, and previous CPR was 70% (n = 126), 7.1 mmol/L (IQR: 3.1-14.0), 2 (IQR: 2-3), and 40% (n = 72), respectively. VA-ECMO was implanted under cardiac compressions in 25% of the patients (n = 46).

TABLE 3. Comparison of pre–VA-ECMO characteristics between survivors and nonsurvivors at 90 days after VA-ECMO initiation

Pre-VA-ECMO characteristics	**MD (%)**	**All patients (n = 181)**	**Survivors (n = 84)**	**Non-survivors (n = 97)**	***P* value**
Gender					
Female	0	45 (25)	23 (51)	22 (49)	-
Male	0	136 (75)	61 (45)	75 (55)	0.466
Age (y)	0	58 (47-66; 11-77)	55 (40-64; 16-76)	61 (50-67; 11-77)	**0.007**
<65 (y)	0	130 (72)	67 (52)	63 (48)	-
≥65 (y)	0	51 (28)	17 (33)	34 (67)	**0.027**
Weight (kg)	0	79 (70-92; 39-143)	80 (68-92; 45-143)	78 (71-93; 39-130)	0.766
BMI (kg/m^2)	0	25.8 (23.4-29.3)	25.6 (23.1-29.0)	25.9 (23.5-29.4)	0.623
Etiology of RCS					
AMI	0	39 (22)	19 (49)	20 (51)	0.744
Postcardiotomy	0	105 (58)	45 (43)	60 (57)	0.260
Other medical*	0	37 (20)	20 (54)	17 (46)	0.296
Ischemic heart disease	0	102 (56)	35 (34)	67 (66)	**<0.001**
Smoking	0	82 (45)	33 (40)	49 (60)	0.130
Hypertension	0	73 (40)	30 (41)	43 (59)	0.239
Chronic renal failure	0	17 (9.4)	6 (35)	11 (65)	0.334
Diabetes mellitus	0	28 (16)	9 (32)	19 (68)	0.100
Dyslipidemia	0	53 (29)	19 (36)	34 (64)	0.067

Atrial fibrillation	0	33 (18)	12 (36)	21 (64)	0.201
Valvular heart disease	0	92 (51)	45 (49)	47 (51)	0.492
Prior†AMI	0	27 (15)	10 (37)	17 (63)	0.290
Prior† PCI	0	16 (8.8)	5 (31)	11 (69)	0.203
Prior† cardiac surgery	0	37 (20)	13 (35)	24 (65)	0.123
Multiorgan failure	0	126 (70)	51 (41)	75 (59)	**0.015**
LVEF (%)‡	0	15 (0-39)	20 (11-50)	13 (0-25)	**<0.001**
≥20 (%)	0	79 (44)	47 (60)	32 (40)	-
<20 (%)	0	102 (56)	37 (36)	65 (64)	**0.002**
MAP (mm Hg)‡	0	54 (44-65)	60 (50-68)	50 (40-60)	**<0.001**
≥50 (mm Hg)	0	118 (65)	66 (56)	52 (44)	-
<50 (mm Hg)	0	63 (35)	18 (29)	45 (71)	**<0.001**
Arterial pH‡	0	7.24 (7.10-7.32; 6.55-7.57)	7.29 (7.17-7.36; 6.63-7.57)	7.20 (7.04-7.30; 6.55-7.49)	**<0.001**
≥7.00	0	158 (87)	79 (50)	79 (50)	-
<7.00	0	23 (13)	5 (22)	18 (78)	**0.011**
Arterial lactate (mmol/L)‡	0	7.1 (3.1-14.0; 0.4-28.0)	4.0 (2.1-9.3; 0.4-20.0)	10.2 (5.2-16.0; 0.7-28.0)	**<0.001**
<5 (mmol/L)	0	69 (38)	47 (68)	22 (32)	-
5-9,9 (mmol/L)	0	47 (26)	22 (47)	25 (53)	-
10-14,9 (mmol/L)	0	29 (16)	9 (31)	20 (69)	-
15-19,9 (mmol/L)	0	24 (13)	5 (21)	19 (79)	-
≥20 (mmol/L)	0	12 (6.6)	1 (8)	11 (92)	**0.004**
<20 (mmol/L)	0	169 (93)	83 (49)	86 (51)	-
≥20 (mmol/L)	0	12 (6.6)	1 (8)	11 (92)	**0.006**
Hemoglobin (g/L)‡	0	100 (89-119)	101 (89-122)	100 (89-117)	0.454
CRP (mg/L)	10	54 (12-158)	53 (10-156)	59 (13-166)	0.553
WBC (10^9/L)	9.4	11.7 (8.0-16.5)	12.4 (8.0-17.3)	11.1 (7.9-15.7)	0.380
Platelets (10^9/L)	6.1	168 (102-234)	173 (106-226)	166 (100-238)	0.978
INR	7.7	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.4 (1.2-1.7)	**0.041**
Creatinine (µmol/L)	1.7	121 (92-166)	116 (80-154)	125 (94-183)	0.126
GFR MDRD (mL/min/1.73m^2)	1.7	53 (39-77)	55 (43-87)	52 (34-72)	0.070
ALT (µkat/L)	7.7	1.29 (0.54-4.90)	0.97 (0.48-4.86)	1.43 (0.59-5.26)	0.296
Pre-VA-ECMO interventions					
Acute PCI	0	43 (24)	19 (44)	24 (56)	0.738
CPR	0	72 (40)	31 (43)	41 (57)	0.462
Hemodialysis	0	31 (17)	14 (45)	17 (55)	0.878
No. of inotropes and vasospressors‡§	0	2 (2-3)	2 (2-3)	3 (2-4)	**0.001**

1	0	31 (17)	20 (65)	11 (35)	-
2	0	64 (35)	33 (52)	31 (48)	-
3	0	47 (26)	20 (43)	27 (57)	-
≥4	0	39 (22)	11 (28)	28 (72)	**0.017**
IABP	0	15 (8.3)	6 (40)	9 (60)	0.603
Retrieved from external hospital	0	64 (35)	29 (45)	35 (55)	0.827
VA-ECMO insertion period¶					
2006-2010	0	93 (51)	38 (41)	55 (59)	-
2011-2015	0	88 (49)	46 (52)	42 (48)	0.124

Bold indicates statistical significance. Categoric variables are presented as n (%) and compared with the chi-square, likelihood ratio, or Fisher exact test. Continuous variables are presented as median (IQR; range) and compared with the Mann–Whitney *U* test. *ALT*, alanine aminotransferase; *AMI*, acute myocardial infarction; *BMI*, body mass index; *CPR*, cardiopulmonary resuscitation; *GFR MDRD*, glomerular filtration rate modification of diet in renal disease; *IABP*, intra-aortic balloon pump; *INR*, international normalized ratio; *LVEF*, left ventricular ejection fraction; *MAP*, mean arterial pressure; *MD*, missing data; *PCI*, percutaneous coronary intervention; *RCS*, refractory cardiogenic shock; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation; *WBC*, white blood cell counts. *Acute decompensated heart failure (n = 29), intoxication (n = 3), acute pulmonary embolus (n = 3), drowning (n = 1), endocarditis (n = 1). †Prior to current medical event/admission. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan. ¶Postimplant variable only for descriptive purposes.

Numerous variables were found significantly associated with 90-day mortality in univariable analysis: age, IHD, multiorgan failure, left ventricular ejection fraction (LVEF), mean arterial pressure (MAP), arterial pH, arterial lactate, INR and number of inotropes and vasopressors (**Table 4A**).

TABLE 4A. Factors associated with mortality within 90 days after VA-ECMO initiation

		Univariable logistic regression			**Multivariable logistic regression**		
Variables	**MD (%)**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Male gender	0	1.29	0.65-2.53	0.466	-	-	-
Age (y)	0	1.03	1.01-1.05	**0.007**	1.03	0.99-1.05	0.055
≥65 vs. <65 (y)	0	2.13	1.08-4.18	**0.029**	-	-	-
Weight (kg)	0	1.01	0.99-1.02	0.598	-	-	-
BMI (kg/m^2)	0	1.02	0.93-1.11	0.736	-	-	-
Etiology of refractory CS							
AMI	0	1.13	0.55-2.29	0.744	-	-	-
Postcardiotomy	0	1.12	0.92-1.37	0.261	-	-	-
Other medical*	0	0.83	0.57-1.19	0.297	-	-	-
Ischemic heart disease	0	3.13	1.70-5.80	**<0.001**	2.90	1.31-6.39	**0.008**
Smoking	0	1.58	0.87-2.85	0.131	-	-	-
Hypertension	0	1.43	0.79-2.61	0.239	-	-	-
Chronic renal failure	0	1.66	0.59-4.71	0.338	-	-	-
Diabetes mellitus	0	2.03	0.86-4.77	0.104	-	-	-
Dyslipidemia	0	1.85	0.96-3.57	0.069	-	-	-
Atrial fibrillation	0	1.66	0.76-3.61	0.203	-	-	-

Valvular heart disease	0	0.67	0.37-1.20	0.177	-	-	-
Prior† myocardial infarction	0	1.57	0.68-3.65	0.292	-	-	-
Prior† PCI	0	2.02	0.67-6.07	0.210	-	-	-
Prior† cardiac surgery	0	1.80	0.85-3.80	0.126	-	-	-
Multiorgan failure	0	2.21	1.16-4.21	**0.016**	1.10	0.48-2.50	0.828
LVEF (%)‡	0	0.97	0.96-0.99	**0.001**	0.99	0.97-1.01	0.248
<20 vs. ≥20 (%)	0	2.58	1.41-4.72	**0.002**	-	-	-
MAP (mmHg)‡	0	0.96	0.94-0.99	**<0.001**	0.99	0.96-1.01	0.387
<50 vs. ≥50 (mmHg)	0	3.17	1.65-6.12	**0.001**	-	-	-
Arterial pH‡	0	0.04	0.01-0.24	**<0.001**	-	-	-
<7.00 vs. ≥7.00	0	3.60	1.27-10.2	**0.016**	-	-	-
Arterial lactate (mmol/L)‡	0	1.15	1.09-1.21	**<0.001**	1.14	1.06-1.23	**<0.001**
<5 (mmol/L)	0	Ref.	-	-	-	-	-
5-9.9 (mmol/L)	0	2.43	1.13-5.22	**0.023**	-	-	-
10-14.9 (mmol/L)	0	4.75	1.86-12.1	**0.001**	-	-	-
15-19.9 (mmol/L)	0	8.12	2.68-24.6	**<0.001**	-	-	-
≥20 (mmol/L)	0	23.5	2.85-193.6	**0.003**	-	-	-
Hemoglobin (g/L)‡	0	1.00	0.98-1.01	0.483	-	-	-
CRP (mg/L)	10	1.00	0.99-1.00	0.320	-	-	-
WBC (10^9/L)	9.4	0.98	0.94-1.01	0.179	-	-	-
Platelets (10^9/L)	6.1	1.00	0.99-1.00	0.635	-	-	-
INR	7.7	1.37	0.91-2.06	0.131	-	-	-
Creatinine (µmol/L)	1.7	1.00	0.99-1.01	0.454	-	-	-
GFR MDRD (mL/min/1.73m^2)	1.7	0.99	0.98-1.00	0.144	-	-	-
ALT (µkat/L)	7.7	1.00	0.98-1.03	0.809	-	-	-
Pre-VA-ECMO interventions							
Acute PCI	0	1.13	0.57-2.24	0.738	-	-	-
CPR	0	1.25	0.69-2.28	0.462	-	-	-
Hemodialysis	0	1.06	0.49-2.31	0.878	-	-	-
Intra-aortic balloon pump	0	1.33	0.45-3.90	0.604	-	-	-
No. of inotropes and vasopressors‡§	0	1.58	1.20-2.10	**0.001**	1.58	1.13-2.21	**0.008**
Retrieved from external hospital	0	1.07	0.58-1.97	0.827	-	-	-
VA-ECMO insertion period							
2011-2015 vs. 2006-2010	0	0.63	0.35-1.14	0.125	-	-	-

Bold indicates statistical significance. *ALT*, alanine aminotransferase; *AMI*, acute myocardial infarction; *BMI*, body mass index; *CI*, confidence interval; *CPR*, cardiopulmonary resuscitation; *CS*, cardiogenic shock; *GFR MDRD*, glomerular filtration rate modification of diet in renal disease; *INR*, international normalized ratio; *LVEF*, left ventricular ejection fraction; *MAP*, mean arterial pressure; *MD*, Missing data; *OR*, odds ratio; *PCI*, percutaneous coronary intervention; *Ref.*, reference; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation; *WBC*, white blood cell counts. *Acute decompensated heart failure (n = 29), intoxication (n = 3), acute pulmonary embolus (n = 3), drowning (n = 1), endocarditis (n = 1). †Prior to current medical event/admission. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan.

In the multivariable logistic regression analysis, only three of the independent variables made a unique statistical significant contribution to the model (**Table 4B**) with the most significant being arterial lactate (odds ratio [OR] per mmol/L: 1.14; 95% confidence interval [CI]: 1.06-1.23, p <0.001), followed by the number of inotropes and vasopressors just before cannulation (OR per one agent: 1.58; 95% CI: 1.13- 2.21; p = 0.008), and the presence of IHD (OR: 2.90; 95% CI: 1.31-6.39; p = 0.008). The full model, containing all independent predictors, was statistical significant, χ^2 (7, n = 181) = 60.979; p <0.001, indicating that the model was able to distinguish between survivors and non-survivors at 90-days. The χ^2 for Hosmer-Lemeshow's Test was 10.256 with a significance level of p = 0.247 thereby supporting our model. The model as a whole explained between 28.6% (Cox and Snell R^2) and 38% (Nagelkerke R^2) of the variance of 90-day mortality and correctly classified 75% of cases. The sensitivity of the model was 78% (the true positives) and its specificity was 71% (the true negatives), giving a positive predictive value of 76% and a negative predictive value of 74%.

TABLE 4B. Factors associated with mortality at 90 days after VA-ECMO initiation

		Univariable logistic regression			**Multivariable logistic regression**		
Variables	**MD (%)**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Arterial lactate (mmol/L)‡	0	1.15	1.09-1.21	**<0.001**	1.14	1.06-1.23	**<0.001**
No. of inotropes and vasopressors‡§	0	1.58	1.20-2.10	**0.001**	1.58	1.13-2.21	**0.008**
Ischemic heart disease	0	3.13	1.70-5.80	**<0.001**	2.90	1.31-6.39	**0.008**

Bold indicates statistical significance. *CI*, confidence interval; *MAP*, mean arterial pressure; *MD*, missing data; *OR*, odds ratio; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan.

Regarding the possible significance of cannulation site, type of VA-ECMO cannulation (peripheral and central VA-ECMO cannulation in 85% [n = 153] and 15% [n = 28] of patients, respectively), surgical cannulation technique (surgical cut down or percutaneous approach) and the presence of distal perfusion catheter (71% of patients [n = 128] with peripheral cannulation) for 90-day mortality, these factors were not included in the statistical analysis as they are considered after the decision has been made to initiate VA-ECMO. The aim of **Study I** was to identify specifically pre-implant predictors for 90-day mortality by not mixing pre-implant with implant and post-implant factors (to potentially provide tools to clinicians deciding whether to institute VA-ECMO) which otherwise would have included

also other factors than the above-mentioned. However, for clarification, the difference between survivors and non-survivors and the logistic regression analysis were non-significant regarding cannulation site or type of cannulation, as presented in **Table 5A** and **Table 5B**.

TABLE 5A. Cannulation sites and comparison between survivors and non-survivors at 90 days after VA-ECMO initiation

Cannulation sites	MD (%)	All patients (n = 181)	Survivors (n = 84)	Non-survivors (n = 97)	*P* value
Operating room	0	146 (81)	66 (45)	80 (55)	0.507
Catherization laboratory	0	13 (7.2)	5 (38)	8 (62)	0.551
Intensive care unit	0	22 (12)	13 (59)	9 (41)	0.203

MD, missing data; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation.

TABLE 5B. Cannulation site associated with 90 day mortality after VA-ECMO initiation

		Univariable logistic regression			Multivariable logistic regression		
Cannulation sites	**MD (%)**	**OR**	**95% CI**	***P* value**	**OR**	**95%CI**	***P* value**
Operating room	0	1.28	0.61-2.67	0.508	-	-	-
Catherization laboratory	0	1.42	0.45-4.52	0.553	-	-	-
Intensive care unit	0	0.56	0.23-1.38	0.208	-	-	-

CI, confidence intreval; *MD* missing data*; OR*, odds ratio; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation

Outcome data including events on and after VA-ECMO and causes of death within 90 days after initiation of VA-ECMO support are presented in **Table 6**. The median duration on VA-ECMO was 7 days (IQR: 3-13). Death during VA-ECMO support occurred in 46% (n = 84) of the patients, 45% (n = 82) were successfully weaned, 8% (n = 15) did not tolerate weaning whereof 11 patients (6%) were bridged to heart transplantation and 4 patients (2%) were bridged to LVAD. The in-hospital mortality was 54% (n = 97) and 46% (n = 84) were discharged to home. The overall 90-day mortality after initiation of VA-ECMO was 54% (n = 97). Multiorgan failure was the main cause of death on VA-ECMO (38 of 84 deaths, 45%), as well as within 90 days after initiation of VA-ECMO (43 of 97 deaths, 44%).

TABLE 6. Outcomes

Variables	MD (%)	All patients (n = 181)
VA-ECMO duration (days)	0	7 (3-13; 0.02-55)
Acute myocardial infarction (n = 39)	0	5 (2-10; 0.08-51)
Postcardiotomy (n = 105)	0	7 (3-14; 0.02-55)
Other medical* (n = 37)	0	6 (1-15; 0.04-46)
VA-ECMO destination		
Death during VA-ECMO	0	84 (46)
Successful weaning	0	82 (45)
VA-ECMO to heart transplantation	0	11 (6.1)

VA-ECMO to LVAD	0	4 (2.2)
90-day mortality	0	97 (54)
Acute myocardial infarction (n = 39)	0	20 (51)
Postcardiotomy (n = 105)	0	60 (57)
Other medical (n = 37)	0	17 (46)
In-hospital mortality, non-discharged	0	97 (54)
Acute myocardial infarction (n = 39)	0	20 (51)
Postcardiotomy (n = 105)	0	59 (56)
Other medical* (n = 37)	0	18 (49)
Discharge to home	0	84 (46)
Acute myocardial infarction (n = 39)	0	19 (49)
Postcardiotomy (n = 105)	0	46 (44)
Other medical* (n = 37)	0	19 (51)
Days from VA-ECMO initiation to discharge home	0	57 (35-97; 13-295)
Main cause of death during VA-ECMO	0	84 (46)
Multiorgan failure	0	38 (21)
Neurologic†	0	23 (13)
Cardiac‡	0	10 (5.5)
Bleeding§	0	10 (5.5)
Miscellaneous¶	0	3 (1.7)
Main cause of death within 90 days	0	97 (54)
Multiorgan failure	0	43 (24)
Neurologic†	0	26 (14)
Cardiac‡	0	13 (7.2)
Bleeding§	0	10 (5.5)
Miscellaneous¶¥	0	5 (2.8)

Categoric and continuous variables are presented as n (%) and median (IQR); range), respectively. *LVAD*, left ventricular assist device; *MD*, missing data; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation; *Other medical etiologies: acute decompensated heart failure (n = 29), intoxication (n = 3), acute pulmonary embolus (n = 3), drowning (n = 1), endocarditis (n = 1). †Stroke, fatal anoxia, brain death. ‡Sudden cardiac arrest, arrhythmia, myocardial infarction, heart failure. §Lung, gastrointestinal, and retroperitoneal bleeding. ¶Acute decompensated heart failure not being a candidate for combined heart-lung transplantation (n = 1), iatrogenic air entry into the VA-ECMO-circuit (n = 1), aortic dissection secondary to initial peripheral cannulation (n = 1). ¥Acute massive pulmonary embolism (n = 1), acute pulmonary embolism and ischemic colitis (n = 1).

Figure 2 illustrates the cumulative Kaplan-Meier survival curve until 90 days after initiation of VA-ECMO support in 181 patients with refractory cardiogenic shock.

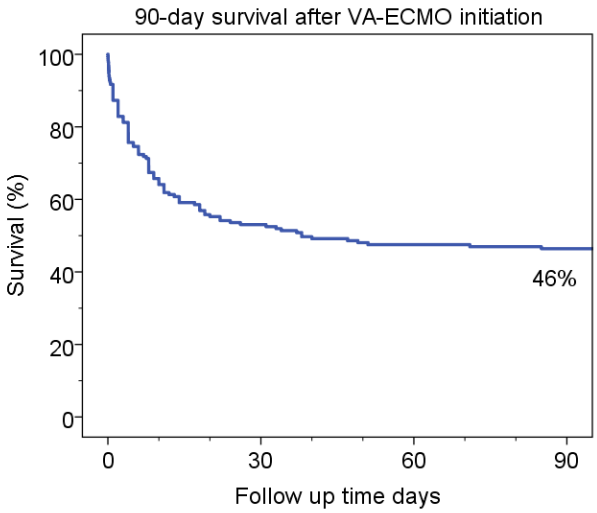

FIGURE 2. Kaplan Meier survival curve until 90 days after venoarterial extracorporeal membrane oxygenation (VA-ECMO) initiation in 181 patients with refractory cardiogenic shock.

Figure 3 depicts the cumulative Kaplan-Meier survival curves until 90 days related to (A) arterial lactate intervals, (B) numbers of inotropes and vasopressors, and (C) presence of IHD before VA-ECMO initiation in 181 patients with refractory cardiogenic shock. Each of the three variables presented a significant drop in survival, most prominent already within the first 10-20 days after initiation of VA-ECMO. The subgroups of arterial lactate intervals and number of inotropes and vasopressors both indicated that the higher the number of agents and the higher the arterial lactate level, the worse the 90-day outcome.

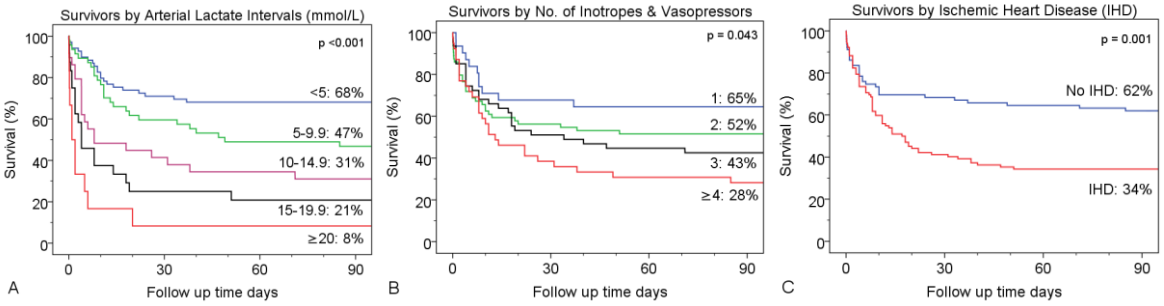

FIGURE 3. Independent pre-VA-ECMO predictors of 90-day mortality. Kaplan-Meier survival curves until 90 days after VA-ECMO initiation related to **(A)** arterial lactate intervals, **(B)** numbers of inotropes and vasopressors, and **(C)** presence of ischemic heart disease just before VA-ECMO initiation in 181 patients with refractory cardiogenic shock. *No. of inotropes & vasopressors*, epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation.

The main complications after initiation of VA-ECMO are presented in **Figure 4** for descriptive purposes but not included in the statistical analysis as they were not pre-VA-

ECMO factors. The most frequent post-implant complication being renal failure necessitating hemodialysis (60%), pneumonia (51%), and sepsis (24%). Moreover, two out of the 181 patients (1.1%) received left ventricular decompression by placement of a transseptal left atrial cannula during VA-ECMO. Both patients died on VA-ECMO. However, left ventricular decompression during VA-ECMO is an on-VA-ECMO variable, and was therefore not included in the analyses of this thesis.

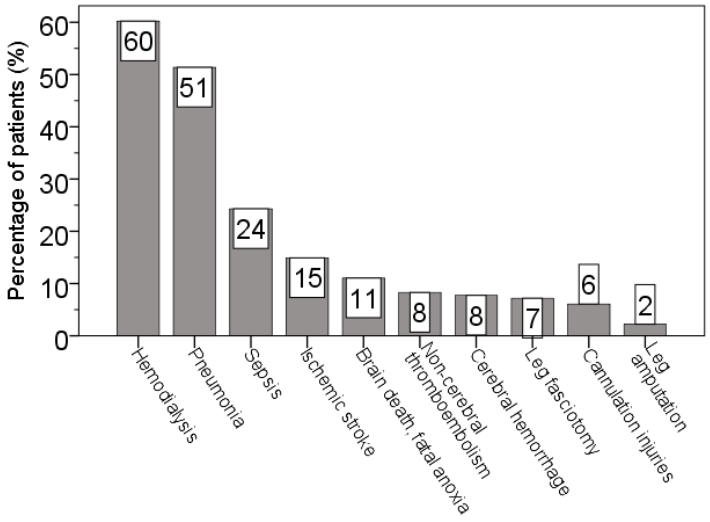

FIGURE 4. Main complications after venoarterial extracorporeal membrane oxygenation initiation in 181 patients with refractory cardiogenic shock.

4.2 STUDY II

Table 7 presents the pre-VA-ECMO variables and the comparison between survivors and non-survivors at 90-days after VA-ECMO initiation. Median age was 62 years (IQR: 52-68). This was significantly lower in survivors (60 years; IQR: 49-66) compared with non-survivors (65 years; IQR: 54-69; p = 0.017). In contrast to the other surgical subgroups, only isolated CABG differed significantly between survivors and non-survivors, with a 90-day mortality of 86%. AMI and IHD was found in 27% (n = 28) and 57% (n = 60) of the patients with an 82% and 77% 90-day mortality, respectively. Median LVEF, arterial pH and MAP just before cannulation were significantly lower among non-survivors compared with survivors. In contrast, age, euroSCORE II, prior CABG, arterial lactate, alanine aminotransferase (ALT) and total number of inotropes and vasopressors (epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan) were significantly higher among non-survivors compared with survivors.

TABLE 7. Comparison of pre-VA-ECMO characteristics between survivors and non-survivors at 90 days after VA-ECMO initiation

Pre-VA-ECMO characteristics	**MD (%)**	**All patients (n = 105)**	**Survivors (n = 45)**	**Non-survivors (n = 60)**	***P* value**
Male gender	0	80 (76)	33 (41)	47 (59)	0.552
Age (y)	0	62 (52-68; 18-77)	60 (49-66; 18-72)	65 (54-69; 23-77)	**0.017**
≥65 (y)	0	42 (40)	13 (31)	29 (69)	**0.044**
Weight (kg)	0	80 (72-93; 45-143)	84 (74-93; 45-143)	78 (72-94; 56-130)	0.441
BMI (kg/m^2)	0	26.2 (23.7-29.8)	26.5 (23.6-30.2)	25.9 (23.7-29.5)	0.669
euroSCORE II score	0	7.32 (2.82-25.03; 0.62-77.53)	4.82 (2.19-21.97; 0.62-43.52)	10.04 (3.53-28.43; 0.92-78.53)	**0.046**
euroSCORE II critical preoperative state	0	38 (36)	16 (42)	22 (58)	0.907
euroSCORE II type of cardiac surgical subgroup					
Single non-CABG	0	30 (29)	16 (53)	14 (47)	0.170
Isolated CABG	0	21 (20)	3 (14)	18 (86)	**0.003**
2 procedures*	0	33 (31)	16 (49)	17 (51)	0.582
3 procedures*	0	21 (20)	10 (48)	11(52)	0.622
euroSCORE II urgency of surgery					
Elective	0	48 (46)	25 (52)	23 (48)	0.080
Urgent	0	19 (18)	8 (42)	11 (58)	0.942
Emergency	0	27 (26)	9 (33)	18 (67)	0.246
Salvage	0	11 (11)	3 (27)	8 (73)	0.345
Type of cardioplegia					
No cardioplegia	0	14 (13)	7 (50)	7 (50)	0.562
Antegrade cardioplegia	0	43 (41)	17 (40)	26 (60)	0.817
Antegrade + retrograde cardioplegia	0	43 (41)	19 (44)	24 (56)	0.819
Retrograde cardioplegia	0	5 (4.8)	2 (40)	3 (60)	1.000
Cross-clamp time (min)	2.9	122 (59-198; 21-359)	136 (84-201; 24-359)	98 (55-193; 21-291)	0.162
CPB time (min)	2.9	222 (172-283; 35-568)	217 (185-275; 35-556)	227 (167-287; 81-568)	0.869
From CPB direct to VA-ECMO in the OR	0	51 (49)	21 (41)	30 (59)	0.735
AMI	0	28 (27)	5 (18)	23 (82)	**0.002**
Ischemic heart disease	0	60 (57)	14 (23)	46 (77)	**<0.001**
Smoking	0	54 (51)	20 (37)	34 (63)	0.215
Hypertension	0	51 (49)	20 (39)	31 (61)	0.464
Valvular heart disease	0	72 (69)	34 (47)	38 (53)	0.182
Congestive heart failure	0	32 (31)	14 (44)	18 (56)	0.903

Diabetes mellitus	0	17 (16)	5 (29)	12 (71)	0.221
Atrial fibrillation	0	26 (25)	9 (35)	17 (65)	0.328
Dyslipidemia	0	36 (34)	13 (36)	23 (64)	0.313
Prior† myocardial infarction	0	20 (19)	6 (30)	14 (70)	0.197
Prior† PCI	0	11 (10)	3 (27)	8 (73)	0.345
Prior† cardiac surgery	0	28 (27)	10 (36)	18 (64)	0.372
Prior† CABG	0	12 (11)	2 (17)	10 (83)	**0.040**
Chronic renal failure	0	14 (13)	4 (29)	10 (71)	0.246
Hypertrophic cardiomyopathy	0	14 (13)	4 (29)	10 (71)	0.246
Endocarditis	0	8 (7.6)	5 (62)	3 (38)	0.243
Primary graft failure after heart transplantation	0	7 (6.7)	4 (57)	3 (43)	0.232
Acute pulmonary embolism	0	2 (1.9)	1 (50)	1 (50)	1.000
LVEF (%)‡	0	25 (13-50)	33 (18-55)	15 (0-29)	**<0.001**
<20 (%)	0	50 (48)	12 (24)	38 (76)	**<0.001**
MAP (mmHg)‡	0	50 (40-64)	60 (49-68)	47 (40-60)	**0.001**
<50 (mmHg)	0	44 (42)	11 (25)	33 (75)	**0.002**
Arterial pH‡	0	7.26 (7.13-7.32; 6.75-7.49)	7.29 (7.18-7.35; 6.84-7.46)	7.22 (7.09-7.31; 6.75-7.49)	**0.009**
Arterial lactate (mmol/L)‡	0	7.0 (3.2-11.5; 0.7-28.0)	4.0 (2.0-8.6; 0.7-14.7)	8.0 (5.4-14.9; 0.7-28.0)	**<0.001**
<5 (mmol/L)	0	39 (37)	25 (64)	14 (36)	-
5-9.9 (mmol/L)	0	36 (34)	16 (44)	20 (56)	-
10-14.9 (mmol/L)	0	16 (15)	4 (25)	12 (75)	-
≥15 (mmol/L)	0	14 (13)	0 (0)	14 (100)	**<0.001**
Hemoglobin (g/L)‡		93 (86-106)	94 (85-109)	93 (86-104)	0.964
WBC (10^9/L)	0	10.8 (7.2-15.7)	10.4 (7.2-16.7)	11.2 (7.2-14.8)	0.568
Platelets (10^9/L)	0	161 (95-234)	157 (108-228)	161 (87-240)	0.991
Creatinine (µmol/L)	0	120 (92-169)	110 (79-159)	124 (95-189)	0.103
GFR MDRD (mL/min/1.73m^2)	0	55 (37-73)	62 (41-89)	53 (33-70)	0.074
ALT (µkat/L)	5.7	0.82 (0.40-2.11)	0.69 (0.34-1.32)	1.06 (0.54-2.80)	**0.041**
Pre-VA-ECMO interventions					
Acute PCI	0	7 (6.7)	2 (29)	5 (71)	0.696
Hemodialysis	0	24 (23)	10 (42)	14 (58)	0.893
CPR	0	31 (30)	12 (39)	19 (61)	0.578
Intra-aortic balloon pump	0	5 (4.8)	1 (20)	4 (80)	0.389

No. of inotropes and vasopressors‡§	0	3 (2-4)	2 (2-3)	3 (2-4)	**0.046**
Retrievel from external hospital	0	24 (23)	8 (33)	16 (67)	0.283
VA-ECMO insertion period¶					
2006-2010	0	55 (52)	19 (35)	36 (65)	-
2011-2015	0	50 (48)	26 (52)	24 (48)	0.071

Bold indicates statistical significance. Categoric variables are presented as n (%) and compared with the chi-square, likelihood ratio, or Fisher exact test. Continuous variables are presented as median (IQR; range) and compared with the Mann–Whitney *U* test. *ALT*, alanine aminotransferase; *AMI*, acute myocardial infarction; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *CPB*, cardiopulmonary bypass; *CPR;* cardiopulmonary resuscitation; *euroSCORE*, European System for Cardiac Operative Risk Evaluation*; GFR MDRD*, glomerular filtration rate modification of diet in renal disease; *LVEF*, left ventricular ejection fraction; *MAP*, mean arterial pressure; *MD*, missing data; *OR* operating room; *PCI*, percutaneous coronary intervention; *VA-ECMO*, venoarterial membrane oxygenation; *WBC*, white blood cell counts. *Number of surgical interventions on the heart (euroSCORE II classification). †Prior to current medical event/admission. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan. ¶Postimplant variable only for descriptive purposes.

Univariable logistic regression identified 8 variables that were significantly associated with 90-day mortality: age, isolated CABG, AMI, IHD, LVEF, MAP, arterial pH and lactate (**Table 8A**). Arterial pH and lactate correlated strongly (rho = - 0.713; p <0.001), as did AMI and IHD (rho = 0.522; p <0.001), CABG and IHD (rho = 0.433; p <0.001), and CABG and AMI (rho = 0.829; p <0.001), respectively. AMI and CABG, both included in the variable IHD, together with arterial pH were excluded from the model. This left five variables in the model. We favored exclusion of pH and not lactate, as lactate can be considered to be a more robust variable as it is less sensitive to the influence of $PaC0_2$ and administration of buffer solutions in the emergency setting.

TABLE 8A. Factors associated with mortality within 90 days after VA-ECMO initiation

		Univariable logistic regression			**Multivariable logistic regression**		
Variables	**MD (%)**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Male gender	0	1.32	0.53-3.24	0.552	-	-	-
Age (y)	0	1.04	1.01-1.07	**0.017**	1.04	0.99-1.09	0.058
≥65 vs. <65 (y)	0	2.30	1.01-5.23	**0.046**	-	-	-
Weight (kg)	0	1.00	0.98-1.02	0.970	-	-	-
BMI (kg/m^2)	0	0.99	0.92-1.07	0.800	-	-	-
euroSCORE II	0	1.03	0.99-1.05	0.071	-	-	-
euroSCORE II critical preoperative state	0	1.05	0.47-2.35	0.907	-	-	-
euroSCORE II type of cardiac surgery							
Single non-CABG	0	0.55	0.24-1.30	0.173	-	-	-
Isolated CABG	0	6.00	1.64-21.9	**0.007**	-	-	-

2 procedures*	0	0.72	0.31-1.64	0.431	-	-	-
3 procedures*	0	0.62	0.30-2.05	0.622	-	-	-
euroSCORE II urgency of surgery							
Elective	0	0.50	0.23-1.09	0.081	-	-	-
Urgent	0	1.04	0.38-2.84	0.942	-	-	-
Emergency	0	1.71	0.69-4.28	0.249	-	-	-
Salvage	0	2.15	0.54-8.63	0.279	-	-	-
Type of cardioplegia							
No cardioplegia	0	Ref.	-	-	-	-	-
Antegrade cardioplegia	0	1.53	0.46-5.14	0.492	-	-	-
Antegrade + retrograde cardioplegia	0	1.26	0.38-4.23	0.705	-	-	-
Retrograde cardioplegia	0	1.50	0.19-11.93	0.702	-	-	-
Cross clamp time (min)	2.9	1.00	0.99-1.00	0.206	-	-	-
CPB time (min)	2.9	1.00	0.99-1.00	0.738	-	-	-
From CPB direct to VA-ECMO in the OR	0	1.14	0.53-2.48	0.735	-	-	-
AMI	0	4.97	1.71-14.4	**0.003**	-	-	-
Ischemic heart disease	0	7.28	3.05-17.4	**<0.001**	7.87	2.55-24.3	**<0.001**
Smoking	0	1.64	0.75-3.56	0.216	-	-	-
Hypertension	0	1.33	0.62-2.90	0.464	-	-	-
Valvular heart disease	0	0.56	0.24-1.32	0.184	-	-	-
Congestive heart failure	0	0.95	0.41-2.20	0.903	-	-	-
Diabetes mellitus	0	2.00	0.65-6.16	0.227	-	-	-
Atrial fibrillation	0	1.58	0.63-3.97	0.330	-	-	-
Dyslipidemia	0	1.53	0.67-3.50	0.314	-	-	-
Prior† myocardial infarction	0	1.98	0.69-5.64	0.202	-	-	-
Prior† PCI	0	2.15	0.54-8.63	0.279	-	-	-
Prior† cardiac surgery	0	1.50	0.61-3.67	0.374	-	-	-
Prior† CABG	0	4.30	0.89-20.7	0.069	-	-	-
Chronic renal failure	0	2.05	0.60-7.02	0.253	-	-	-
Hypertrophic cardiomyopathy	0	2.05	0.60-7.02	0.253	-	-	-
Endocarditis	0	0.42	0.10-1.86	0.254	-	-	-
Primary graft failure after heart transplantation	0	0.54	0.12-2.54	0.435	-	-	-
LVEF (%)‡	0	0.96	0.94-0.98	**<0.001**	0.98	0.95-1.01	0.112
<20 vs. ≥20 (%)	0	4.75	2.04-11.1	**<0.001**	-	-	-
MAP (mmHg)‡	0	0.96	0.94-0.99	**0.007**	0.98	0.95-1.04	0.243

<50 vs. ≥50 (mmHg)	0	3.78	1.62-8.83	**0.002**	-	-	-
Arterial pH‡	0	0.03	0.00-0.53	**0.017**	-	-	-
Arterial lactate (mmol/L)‡	0	1.21	1.10-1.33	**<0.001**	1.22	1.07-1.40	**0.004**
Hemoglobin (g/L)‡	0	1.00	0.98-1.02	0.851	-	-	-
WBC (10^9/L)	0	0.97	0.93-1.02	0.269	-	-	-
Platelets (10^9/L)	0	1.00	0.99-1.00	0.576	-	-	-
Creatinine (µmol/L)	0	1.00	0.99-1.01	0.686	-	-	-
GFR MDRD (mL/min/1.73m^2)	0	0.99	0.97-1.00	0.051	-	-	-
ALT (µkat/L)	5.7	1.00	0.97-1.04	0.923	-	-	-
Pre-VA-ECMO interventions	0						
Acute PCI	0	1.96	0.36-10.6	0.436	-	-	-
Hemodialysis	0	1.07	0.42-2.68	0.893	-	-	-
CPR	0	1.27	0.54-3.00	0.579	-	-	-
No. of inotropes and vasopressors‡§	0	1.42	0.99-2.04	0.055	-	-	-
Retrieval from external hospital	0	1.68	0.65-4.37	0.286	-	-	-

Bold indicates statistical significance. *ALT*, alanine aminotransferase; *AMI*, acute myocardial infarction; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *CI*, confidence interval; *CPB*, cardiopulmonary bypass; *CPR*, cardiopulmonary resuscitation; *euroSCORE*, European System for Cardiac Operative Risk Evaluation*; GFR MDRD*, glomerular filtration rate modification of diet in renal disease; *LVEF*, left ventricular ejection fraction; *MAP*, mean arterial pressure; *MD*, missing data; *OR*, odds ratio; *OR* operating room; *PCI*, percutaneous coronary intervention; *VA-ECMO*, venoarterial membrane oxygenation; *WBC*, white blood cell counts. *Number of surgical interventions on the heart (euroSCORE II classification). †Prior to current medical event/admission. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan.

When determining AIC, the original model had a value of 102, compared to 105 (3 knots) and 104 (4 knots). The corresponding BIC values were 118, 131 (3 knots), and 141 (4 knots), respectively. Due to comparable values in both AIC and BIC, the approach of non-linearity through splines did thereby not influence the logistic regression analysis unacceptably. This supported the original model without transformations, which thereby facilitates clinical interpretation of the findings. The model was statistically significant, χ^2 (5, n = 105) = 52.911; p <0.001, indicating that the original model appropriately could discriminate between survivors and non-survivors at 90-days after initiation of VA-ECMO. χ^2 for Hosmer-Lemeshow's Test was 2.952 with a significance level of p = 0.937. This further supported that the overall fit of the model was sufficient. The model as a whole explained between 40% (Cox and Snell R^2) and 53% (Nagelkerke R^2) of the variance of 90-day mortality and overall correctly classified 80% of the cases. The original model's sensitivity and specificity was 85% (true positives) and 73% (true negatives), respectively, resulting in a positive predictive value of 81% and a negative predictive value of 79%.

Two of the independent variables significantly contributed to the model (**Table 8B**) in multivariable logistic regression analysis. Presence of IHD was the most significant predictor of 90-day mortality (OR: 7.87; 95% CI: 2.55-24.3; p <0.001), followed by arterial lactate (OR per mmol/L increase: 1.22; 95% CI: 1.07-1.40, p = 0.004).

TABLE 8B. Factors associated with mortality at 90 days after VA-ECMO initiation

		Univariable logistic regression			Multivariable logistic regression		
Variables	**MD (%)**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Age (y)	0	1.04	1.01-1.07	**0.017**	1.04	0.99-1.09	0.058
Ischemic heart disease	0	7.28	3.05-17.4	**<0.001**	7.87	2.55-24.3	**<0.001**
LVEF (%)‡	0	0.96	0.94-0.98	**<0.001**	0.98	0.95-1.01	0.112
MAP (mmHg)‡	0	0.96	0.94-0.99	**0.007**	0.98	0.95-1.04	0.243
Arterial lactate (mmol/L)‡	0	1.21	1.10-1.33	**<0.001**	1.22	1.07-1.40	**0.004**

Bold indicates statistical significance. *CI,* confidence interval; *LVEF,* left ventricular ejection fraction; *MAP,* mean arterial pressure; *MD,* missing data; *OR,* odds ratio; *VA-ECMO,* venoarterial membrane oxygenation. ‡Just before cannulation.

Table 9 demonstrates outcome data including events after initiation of VA-ECMO and causes of death within 90 days. The median duration of VA-ECMO was 7 days (IQR: 3-14). Forty-nine patients (47%) died during VA-ECMO, 54 patients (51%) were successfully weaned, two patients (2%) could not be weaned, one patient (1%) was bridged to heart transplantation and one patient (1%) was bridged to LVAD. The in-hospital mortality was 56% (n = 59) and 44% (n = 46) were discharged home. The median number of days from initiation of VA-ECMO to discharge home was 64 (IQR: 41-105; range 13-212). The overall 90-day mortality after initiation of VA-ECMO, which was the primary endpoint, was 57% (n = 60). The overall mortality at 24, 48, 72 hours, 7, and 30 days were 11%, 11%, 15%, 25% and 51%, respectively. Multiorgan failure was the main cause of death both on VA-ECMO (24 of 49 deaths, 49%) and within 90 days after its initiation (29 of 49 deaths, 59%). The 90-day mortality in patients with peripheral (76%, n = 80) and central cannulation (24%, n = 25) was 51% and 76%, respectively. Seventy-two patients (90%) with peripheral cannulation received an extra distal perfusion cannula for antegrade perfusion of the leg (shunt).

TABLE 9. Outcomes

Variables	**MD (%)**	**All patients (n = 105)**
VA-ECMO duration (days)	0	7 (3-14; 1-55)
Single non-CABG (n = 30)	0	8 (4-25)
Isolated CABG (n = 21)	0	6 (2-11)
2 Procedures* (n = 33)	0	9 (5-17)
3 Procedures* (n = 21)	0	5 (3-11)
VA-ECMO destination		

Death during VA- ECMO	0	49 (47)
Successful weaning	0	54 (51)
VA-ECMO to heart transplantation	0	1 (1.0)
VA-ECMO to LVAD	0	1 (1.0)
90-day mortality	0	60 (57)
Single non-CABG (n = 30)	0	14 (47)
Isolated CABG (n = 21)	0	18 (86)
2 Procedures* (n = 33)	0	17 (52)
3 Procedures* (n = 21)	0	11 (52)
In-hospital mortality	0	59 (56)
Single non-CABG (n = 30)	0	13 (43)
Isolated CABG (n = 21)	0	18 (86)
2 Procedures* (n = 33)	0	17 (52)
3 Procedures* (n = 21)	0	11 (52)
Discharge to home	0	46 (44)
Single non-CABG (n = 30)	0	17 (57)
Isolated CABG (n = 21)	0	3 (14)
2 Procedures* (n = 33)	0	16 (49)
3 Procedures* (n = 21)	0	10 (48)
Days from VA-ECMO initiation to discharge home	0	64 (41-105; 13-212)
CPC score at discharge to home	0	46 (44)
CPC 1-2	0	46 (100)
CPC 3-4	0	0 (0)
Main cause of death during VA-ECMO	0	49 (47)
Multiorgan failure	0	24 (23)
Neurologic†	0	9 (8,6)
Cardiac‡	0	7 (6.7)
Bleeding§	0	7 (6.7)
Miscellaneous¶	0	2 (1.9)
Main cause of death within 90 days	0	60 (57)
Multiorgan failure	0	29 (28)
Neurologic†	0	12 (11)
Cardiac‡	0	8 (7.6)
Bleeding§	0	7 (6.7)
Miscellaneous¶¥	0	4 (3.8)

Categorical and continuous variables are presented as n (%) and median (interquartile range (IQR); range), respectively. *CABG*, coronary artery bypass grafting; *CPC*, cerebral performance category; *LVAD*, left ventricular assist device; *MD*, missing data*; VA-ECMO*, venoarterial extracorporeal membrane oxygenation. *Number of surgical interventions on the heart (euroSCORE II classification). †Stroke, fatal anoxia, brain death. ‡Sudden cardiac arrest, arrhythmia, myocardial infarction, heart failure. §Lung, gastrointestinal, retroperitoneal bleeding. ¶Iatrogenic air entry into the VA-ECMO-circuit (n = 1), aortic dissection at cannulation (n = 1). ¥Massive pulmonary embolus (n = 1), pulmonary embolus and ischemic colitis (n = 1).

The cumulative Kaplan-Meier survival curves until 90 days after initiation of VA-ECMO related to arterial lactate intervals are presented in **Figure 5A**, which suggests that an arterial lactate level ≥10 mmol/L (90.1 mg/dL) had severely worse outcome (p <0.001). All patients with an arterial lactate level ≥15 mmol/L (135 mg/dL) died within 20 days after VA-ECMO initiation. The cumulative 90-day survival in patients with IHD was 23% compared with 69% in patients without IHD (p <0.001) **(Figure 5B).**

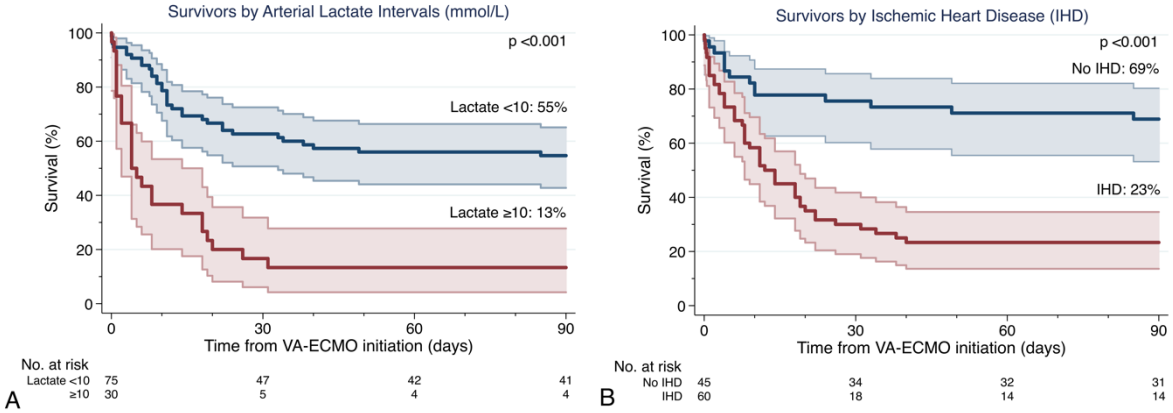

FIGURE 5. Kaplan-Meier survival curves until 90 days after VA-ECMO initiation related to **(A)** arterial lactate intervals, and **(B)** presence of ischemic heart disease, with 95% confidence intervals, at initiation of VA-ECMO in 105 patients with refractory postcardiotomy cardiogenic shock.

The surgical euroSCORE II subgroup isolated CABG, despite not being an independent risk factor of 90-day mortality, had the poorest survival, with a rapid fall during the first 15 days after which it flattened to 14% at 90 days after start of VA-ECMO (p <0.001). Conversely, 90-day survival rates of the remaining three euroSCORE II subgroups (single non-CABG, 2- and 3 concomitant surgical procedures) were close to 50% as illustrated in **Figure 6**.

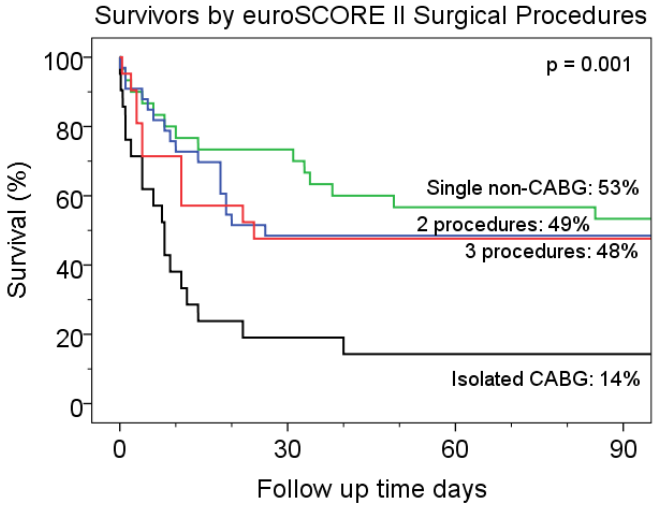

FIGURE 6. Kaplan-Meier survival curves until 90 days after VA-ECMO initiation related to euroSCORE II classification: single non-CABG, 2- and 3 concomitant surgical procedures and isolated CABG, in 105 patients with refractory postcardiotomy cardiogenic shock.

Figure 7 depicts the main complications after VA-ECMO initiation. Renal failure necessitating hemodialysis was the most frequent complication (70%) followed by re-exploration (68%), pneumonia (61%), sepsis (24%), and ischemic stroke (16%).

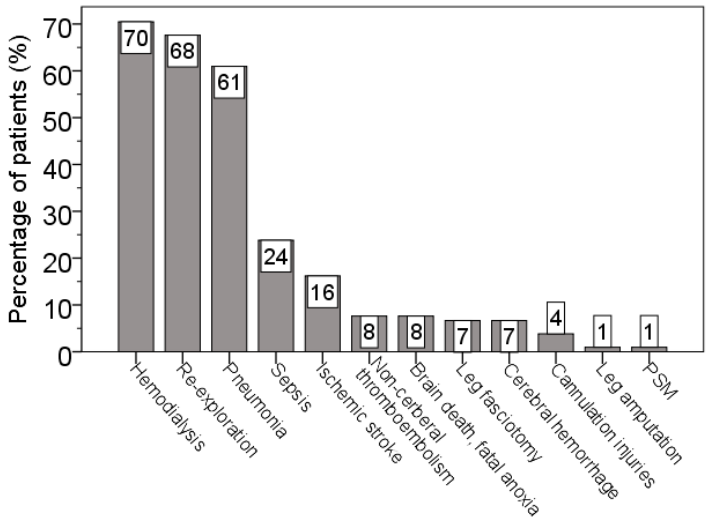

FIGURE 7. Main complications after venoarterial extracorporeal membrane oxygenation initiation in 105 patients with refractory postcardiotomy cardiogenic shock. *PSM*, poststernotomy mediastinitis.

STUDY III

A comparison of pre-VA-ECMO variables between survivors and non-survivors of 76 non-surgical patients at 90 days after initiation of VA-ECMO support is presented in **Table 10**. There were significant differences including arterial lactate, arterial pH, MAP, and number of inotropes and vasopressors just before cannulation. Median age was 52 years (IQR: 37-60) and did not differ significantly between survivors (50 years; IQR: 36-58) and non-survivors (55 years; IQR: 47-60; p = 0.194). Three patients were older than 70 years (the oldest was 76 years old), all being alive at 90 days after VA-ECMO initiation. The most common etiology (mutually exclusive) for VA-ECMO support was AMI (n = 39; 51%) followed by AHF of other etiologies (n = 37; 49%); acute deterioration of chronic cardiomyopathy (n = 13; 17% including idiopathic non-ischemic cardiomyopathy [n = 9; 12%] and ischemic cardiomyopathy [n = 4; 5.3%]), acute myocarditis (n = 10; 13%), acute pulmonary embolus (n = 3; 4%), intoxication (n = 3; 4%), septic cardiomyopathy (n = 3; 4%), peripartum cardiomyopathy (n = 2; 2.6%), severe hypothermia (n = 1; 1.3%), endocarditis (n = 1; 1.3%), and congenital pulmonary valve stenosis (n = 1; 1.3%). Before VA-ECMO implantation, CPR, primary PCI, and support with intra-aortic balloon pump (IABP) was performed in 47% (n =

36), 54% (n = 41) and 24% (n = 18) of patients, respectively. IABP was removed in 10 patients (13%) at VA-ECMO initiation, leaving 8 patients (11%) with IABP during VA-ECMO support. Seven patients (9%) received renal replacement therapy (RRT) before initiation of VA-ECMO and in further 22 patients (29%) RRT was started during VA-ECMO, resulting in totally 35 patients (46%) receiving RRT during VA-ECMO. Mechanical ventilation was applied before implantation in all patients (n = 76). The location of cannulation did not significantly influence 90-day mortality, with 47 patients being cannulated in the operating room (62%, p = 0.955), 18 in the ICU (24%, p = 0.341), and 11 in the catheterization laboratory (15%, p = 0.283). Seventy-six percent of patients with peripheral cannulation (56 of 74) received a distal perfusion catheter.

TABLE 10. Comparison of pre-VA-ECMO characteristics between survivors and non-survivors at 90 days after VA-ECMO initiation

Pre-VA-ECMO characteristics	**MD (%)**	**All patients (n = 76)**	**Survivors (n = 39)**	**Non-survivors (n = 37)**	***P* value**
Male gender	0	56 (74)	28 (50)	28 (50)	0.701
Age (y)	0	52 (37-60; 11-76)	50 (36-58; 16-76)	55 (47-60; 11-70)	0.194
Weight (kg)	0	76 (68-92; 39-110)	79 (67-92; 50-109)	79 (71-93; 44-126)	0.388
BMI	0	25.3 (22.7-29.0)	24.6 (22.6-28.6)	26.5 (22.5-29.4)	0.336
Etiology of refractory CS					
AMI	0	39 (51)	19 (49)	20 (51)	-
Other AHF etiologies*	0	37 (49)	20 (54)	17 (46)	0.642
Acute decompensated chronic CMP	0	13 (17)	8 (62)	5 (38)	0.418
Acute myocarditis	0	10 (13)	7 (70)	3 (30)	0.311
Clinical presentation					
STEMI	0	36 (47)	18 (50)	18 (50)	0.828
NSTEMI	0	3 (3.9)	1 (33)	2 (67)	0.610
Ischemic heart disease	0	42 (55)	21 (50)	21 (50)	0.799
Single vessel CAD	0	14 (18)	7 (50)	7 (50)	1.000
Two vessel CAD	0	4 (5.3)	3 (75)	1 (25)	0.615
Three vessel CAD	0	21 (28)	9 (43)	12 (57)	0.362
Smoking	0	28 (37)	13 (46)	15 (54)	0.515
Hypertension	0	22 (29)	10 (46)	12 (54)	0.514
Valvular heart disease	0	23 (30)	14 (61)	9 (39)	0.272
Dyslipidemia	0	17 (22)	6 (35)	11 (65)	0.134
Diabetes mellitus	0	11 (15)	4 (36)	7 (64)	0.283
Acute myocarditis	0	10 (13)	7 (70)	3 (30)	0.311
Atrial fibrillation	0	7 (9.2)	3 (43)	4 (57)	0.708

Prior† myocardial infarction	0	7 (9.2)	4 (57)	3 (43)	1.000
Prior† PCI	0	5 (6.6)	2 (40)	3 (60)	0.671
Prior† CABG	0	5 (6.6)	1 (20)	4 (80)	0.194
Chronic renal failure	0	3 (3.9)	2 (67)	1 (33)	1.000
LVEF (%)‡	0	11 (0-20)	15 (0-20)	0 (0-20)	0.098
MAP (mmHg)‡	0	55 (48-65)	60 (50-70)	50 (42-60)	**0.015**
Arterial pH‡	0	7.22 (7.01-7.33; 6.55-7.57)	7.29 (7.17-7.37; 6.63-7.57)	7.12 (6.90-7.29; 6.66-7.45)	**0.005**
Arterial lactate (mmol/L)‡	0	7.7 (2.9-15.8; 0.4-27.0)	4.0 (2.2-12.0; 0.4-20.0)	13.0 (5.1-18.6; 0.7-27.0)	**0.002**
<10 (mmol/L)	0	41 (54)	28 (68)	13 (32)	-
10-20 (mmol/L)	0	28 (37)	11 (39)	17 (61)	-
>20 (mmol/L)	0	7 (9.2)	0 (0)	7 (100)	**<0.001**
Hemoglobin (g/L)‡	0	118 (99-131)	118 (98-137)	115 (100-128)	0.647
CRP (mg/L)	9	52 (9-108)	51 (8-98)	54 (9-151)	0.513
WBC (10^9/L)	5	12.4 (9.6-17.4)	12.5 (9.8-17.5)	11.1 (9.2-17.9)	0.530
Platelets (10^9/L)	2	180 (107-235)	183 (105-226)	177 (110-239)	0.858
INR	8	1.4 (1.1-1.6)	1.4 (1.1-1.9)	1.4 (1.1-1.6)	0.604
Creatinine (µmol/L)	2	127 (86-160)	129 (81-148)	126 (87-165)	0.592
GFR MDRD (mL/min/1.73m^2)	2	52 (40-86)	52 (43-87)	52 (36-85)	0.469
ALT (µkat/L)	8	3.24 (0.90-10.70)	3.61 (0.90-10.58)	3.04 (0.99-11.50)	1.000
Pre-VA-ECMO interventions					
Primary PCI	0	36 (47)	17 (47)	19 (53)	0.498
Successful PCI	0	22 (61)	11 (50)	11 (50)	0.994
Intra-aortic balloon pump	0	18 (24)	7 (39)	11 (61)	0.227
CPR	0	41 (54)	19 (46)	22 (54)	0.348
Hemodialysis	0	7 (9.2)	4 (57)	3 (43)	1.000
No. of inotropes and vasopressors‡§	0	2 (2-3)	2 (1-3)	2 (2-3)	**0.015**
1	0	17 (22)	13 (77)	4 (23)	-
2	0	33 (43)	16 (48)	17 (52)	-
≥3	0	26 (34)	10 (38)	16 (62)	**0.047**
Retrieval from external hospital	0	40 (53)	21 (52)	19 (48)	0.828
VA-ECMO insertion period¶					
2006-2010	0	38 (50)	19 (50)	19 (50)	-
2011-2015	0	38 (50)	20 (53)	18 (47)	0.818

Bold indicates statistical significance. Categorical variables are presented as numbers (n) and percentages (%), and compared with the Chi-square, Likelihood ratio or Fischer's exact test. Continuous variables are presented as median (interquartile range (IQR); range) and compared with the Mann-Whitney *U* test. *AHF*, acute heart failure; *ALT*, alanine aminotransferase; *AMI;* acute myocardial infarction; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CMP*, cardiomyopathy; *CPR*, cardiopulmonary resuscitation; *CS*, cardiogenic shock; *GFR MDRD*, glomerular filtration rate modification of diet in renal disease; *INR*, international normalized ratio; *LVEF*, left ventricular ejection fraction; *MAP*, mean arterial pressure; *MD*, missing data; *NSTEMI*, non-ST-elevation myocardial infarction; *PCI*, percutaneous coronary; intervention; *STEMI*, ST-elevation myocardial infarction; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation; *WBC*, white blood cell counts.*Acute decompensated chronic cardiomyopathy (n = 13), acute myocarditis (n = 10), intoxication, acute pulmonary embolus, septic cardiomyopathy (each n = 3), peripartum cardiomyopathy (n = 2), prolonged hypothermia, endocarditis, congenital pulmonary valve stenosis (each n = 1).†Prior to current medical event/admission. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan. ¶Postimplant variable only for descriptive purposes.

Four variables were found significantly associated with 90-day mortality in the univariable logistic regression analysis: arterial lactate, arterial pH, number of inotropes and vasopressors, and MAP **(Table 11A)**. Two variables remained significant in the multivariable logistic regression analysis, after exclusion of pH and MAP due to high correlation with lactate (rho = -0.759; p <0.001 and rho = -0.662; p <0.001, respectively), with the most significant being arterial lactate (OR per mmol/L: 1.15; 95% CI: 1.06-1.24; p = 0.001), followed by the number of inotropes and vasopressors (OR per agent: 2.14; 95% CI: 1.26-3.63; p = 0.005).

TABLE 11A. Factors associated with mortality at 90 days after VA-ECMO initiation

		Univariable logistic regression			**Multivariable logistic regression**		
Variables	**MD (%)**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Male gender	0	1.22	0.44-3.41	0.701	-	-	-
Age (y)	0	1.02	0.99-1.05	0.252	-	-	-
Weight (kg)	0	1.01	0.98-1.04	0.510	-	-	-
BMI	0	1.05	0.95-1.17	0.328	-	-	-
Clinical presentation							
AMI	0	1.24	0.50-3.05	0.642	-	-	-
STEMI	0	1.11	0.45-2.72	0.828	-	-	-
Ischemic heart disease	0	1.13	0.46-2.78	0.799	-	-	-
Single vessel CAD	0	1.07	0.33-3.40	0.913	-	-	-
Two vessel CAD	0	0.33	0.03-3.36	0.351	-	-	-
Three vessel CAD	0	1.60	0.58-4.41	0.364	-	-	-
Smoking	0	1.36	0.54-3.47	0.516	-	-	-
Hypertension	0	1.39	0.52-3.77	0.515	-	-	-
Valvular heart disease	0	0.82	0.29-2.28	0.701	-	-	-
Diabetes mellitus	0	2.04	0.54-7.66	0.290	-	-	-
Atrial fibrillation	0	1.46	0.30-6.99	0.640	-	-	-
Dyslipidemia	0	2.33	0.76-7.13	0.139	-	-	-
Prior† myocardial infarction	0	0.77	0.16-3.71	0.747	-	-	-
Prior† PCI	0	1.63	0.26-10.4	0.603	-	-	-

Prior† CABG	0	4.61	0.49-43.3	0.181	-	-	-
Acute myocarditis	0	0.55	0.15-2.08	0.381	-	-	-
Chronic renal failure	0	0.51	0.05-5.92	0.593	-	-	-
LVEF (%)‡	0	0.99	0.97-1.01	0.375	-	-	-
MAP (mmHg)‡	0	0.96	0.93-0.99	**0.036**	-	-	-
Arterial pH‡	0	0.04	0.01-0.37	**0.005**	-	-	-
Arterial lactate (mmol/L)‡	0	1.12	1.05-1.20	**0.002**	1.15	1.06-1.24	**0.001**
Hemoglobin (g/L)‡	0	0.99	0.98-1.02	0.863	-	-	-
CRP (mg/L)	9	1.00	0.99-1.01	0.216	-	-	-
WBC (10^9/L)	5	0.98	0.92-1.04	0.492	-	-	-
Platelets (10^9/L)	2	1.00	0.99-1.01	0.993	-	-	-
INR	8	0.78	0.42-1.44	0.429	-	-	-
Creatinine (µmol/L)	2	1.00	0.99-1.01	0.490	-	-	-
GFR MDRD (mL/min/1.73m^2)	2	0.99	0.99-1.01	0.905	-	-	-
ALT (µkat/L)	8	1.01	0.97-1.05	0.596	-	-	-
Pre-VA-ECMO interventions					-	-	-
Acute PCI	0	1.37	0.55-3.37	0.499	-	-	-
Intra-aortic balloon pump	0	1.06	0.28-4.02	0.929	-	-	-
CPR	0	1.54	0.62-3.83	0.349	-	-	-
Hemodialysis	0	0.77	0.16-3.71	0.747	-	-	-
No. of inotropes and vasopressors‡§	0	1.82	1.12-2.94	**0.015**	2.14	1.26-3.63	**0.005**
Retrieved from external hospital	0	0.91	0.37-2.23	0.828	-	-	-

Bold indicates statistical significance. *ALT*, alanine aminotransferase; *AMI*, acute myocardial infarction; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CI*, confidence interval; *CMP*, cardiomyopathy; *CPR*, cardiopulmonary resuscitation; *GFR MDRD*, glomerular filtration rate modification of diet in renal disease; *INR*, international normalized ratio; *LVEF*, left ventricular ejection fraction; *MAP*, mean arterial pressure; *MD*, missing data; *OR*, odds ratio; *PCI*, percutaneous coronary intervention; *STEMI*, ST-elevation myocardial infarction; *WBC*, white blood cell counts; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation. †Prior to current medical event/admission. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan.

Non-linearity did not impact the logistic regression analysis according to the restricted cubic splines analysis. This favors the use of the model. The original model had a value of 90, compared to 93 (3 knots) and 97 (4 knots) when assessing AIC. The corresponding BIC values were 97, 105 (3 knots), and 113 (4 knots), respectively. As the values in both AIC and BIC were similar, the use of non-linearity through splines did not appear to influence the logistic regression analysis in a pugnacious way, thereby supporting the original model without transformation and facilitating clinical interpretation. The full model with the independent predictors, was statistical significant, χ^2 (df = 2, n = 76) = 21.433; p <0.001, implying that the original model could differ between survivors and non-survivors at 90-days after VA-ECMO

initiation. The χ^2 for Hosmer-Lemeshow's Test was 6.293 with a significance level of p = 0.614 which supported the use of the model. Both the independent variables, arterial lactate and number of inotropes and vasopressors, contributed significantly to the model as shown in **Table 11B**. The model has a sensitivity of 70% (true positives) and a specificity of 67% (true negatives), which positive predictive value of 67% and negative predictive value of 70%.

TABLE 11B. Factors associated with mortality at 90 days after VA-ECMO initiation

		Univariable logistic regression			**Multivariable logistic regression**		
Variables	**MD (%)**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
MAP (mmHg)‡	0	0.96	0.93-0.99	**0.036**	-	-	-
Arterial pH‡	0	0.04	0.01-0.37	**0.005**	-	-	-
Arterial lactate (mmol/L)‡	0	1.12	1.05-1.20	**0.002**	1.15	1.06-1.24	**0.001**
No. of inotropes and vasopressors‡§	0	1.82	1.12-2.94	**0.005**	2.14	1.26-3.63	**0.005**

Bold indicates statistical significance. *CI*, confidence interval; *MAP*, mean arterial pressure; *MD*, missing data; *OR*, odds ratio; *VA-ECMO*, venoarterial membrane oxygenation. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan.

Table 12 presents the outcome data including events after VA-ECMO initiation and causes of death within 90 days. The median duration on VA-ECMO was 5 days (IQR: 2-11; 1-51). Thirty-five patients (46%) died during VA-ECMO support, and 28 patients (37%) were successfully weaned. Weaning failed in 13 patients (17%), 10 patients (13%) were bridged to heart transplantation, and 3 patients (4%) were bridged to LVAD. The in-hospital mortality was 50% (n = 38) and 50% (n = 38) were discharged to home. The mortality rate after 24, 48, 72 hours, 7, 30, 90 days, and 18 months were 16%, 22%, 24%, 33%, 42%, 49%, and 51%, respectively. Of the 38 patients discharged to home, all had a good cerebral functional outcome score, defined as a score of 1-2 according to the Cerebral Performance Category (CPC) scale. Multiorgan failure and brain injuries were the main causes of death on VA-ECMO, 40% (14 of 35 deaths) respectively, as well as within 90 days after initiation of VA-ECMO, 38% (14 of 37 deaths) respectively.

TABLE 12. Outcomes

Variables	**MD (%)**	**All patients (n = 76)**
VA-ECMO duration (days)	0	5 (2-11; 1-51)
AMI (n = 39)	0	5 (2-10)
Other AHF etiologies* (n = 37)	0	6 (1-15)
Acute decompensated chronic CMP (n = 13)	0	7 (3-16)
Myocarditis (n = 10)	0	14 (5-29)
VA-ECMO destination		
Death during VA-ECMO	0	35 (46)

Successful weaning	0	28 (37)
VA-ECMO to heart transplantation	0	10 (13)
VA-ECMO to LVAD	0	3 (3.9)
90-day mortality	0	37 (49)
AMI (n = 39)	0	20 (51)
Other AHF etiologies* (n = 37)	0	17 (46)
Acute decompensated chronic CMP (n = 13)	0	5 (38)
Myocarditis (n = 10)	0	3 (30)
In-hospital mortality	0	38 (50)
AMI (n = 39)	0	20 (51)
Other AHF etiologies* (n = 37)	0	18 (49)
Acute decompensated chronic CMP (n = 13)	0	5 (38)
Myocarditis (n = 10)	0	3 (30)
Discharge to home	0	38 (50)
Days from VA-ECMO initiation to discharge home	0	46 (33-88;13-295)
CPC score at discharge to home	0	38 (50)
CPC 1-2	0	38 (100)
CPC 3-4	0	0 (0)
Cause of death during VA-ECMO	0	35 (46)
Multiorgan failure	0	14 (18)
Neurological†	0	14 (18)
Cardiac‡	0	3 (3.9)
Bleeding§	0	3 (3.9)
Miscellaneous¶	0	1 (1.3)
Cause of death within 90 days	0	37 (49)
Multiorgan failure	0	14 (18)
Neurological†	0	14 (18)
Cardiac‡	0	3 (3.9)
Bleeding§	0	5 (6.6)
Miscellaneous¶	0	1 (1.3)

Categorical and continuous variables are presented as numbers (n), percentages (%), and median (interquartile range (IQR); range), respectively. *AHF*, acute heart failure; *AMI*, acute myocardial infarction; *CMP*, cardiomyopathy; *CPC*, cerebral performance category; *LVAD*, left ventricular assist device; *MD*, missing data; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation. *Acute decompensated chronic cardiomyopathy (n = 13), acute myocarditis (n = 10), intoxication, acute pulmonary embolus, septic cardiomyopathy (each n = 3), peripartum cardiomyopathy (n = 2), prolonged hypothermia, endocarditis, congenital pulmonary valve stenosis (each n = 1). †Stroke, fatal anoxia, brain death. ‡Sudden cardiac arrest, myocardial infarction, heart failure. §Lung, gastrointestinal, retroperitoneal. ¶Terminal emphysema.

The cumulative Kaplan-Meier survival curves until 90 days after initiation of VA-ECMO related to the arterial lactate intervals are presented in **Figure 8** and suggest that the higher the arterial lactate level, the worse the survival ($p < 0.001$). The three curves display a significant fall in survival mainly within the first 10 days after VA-ECMO initiation. All patients (7 of

7) with a pre-VA-ECMO lactate level higher than 20mmol/L died within six days after initiation of VA-ECMO.

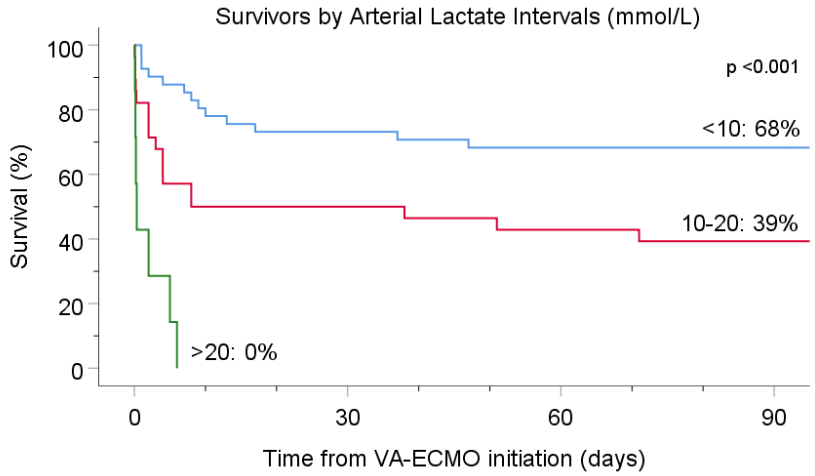

FIGURE 8. Kaplan-Meier survival curves until 90 days after VA-ECMO initiation related to arterial lactate intervals in 76 patients with non-surgical refractory cardiogenic shock. *VA-ECMO*, venoarterial extracorporeal membrane oxygenation.

Figure 9 illustrates the main complications after initiation of VA-ECMO with the most frequent being renal failure necessitating hemodialysis (46%), pneumonia (38%), sepsis (25%), and brain death or fatal anoxia (16%).

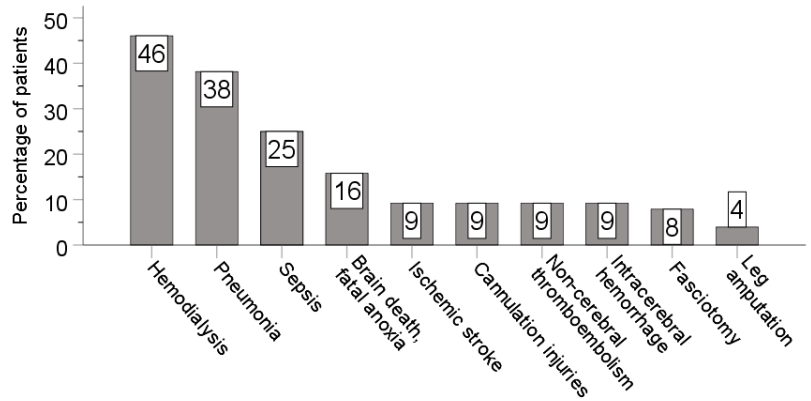

FIGURE 9. Main complications after venoarterial extracorporeal membrane oxygenation initiation in 76 patients with non-surgical refractory cardiogenic shock.

4.3 STUDY IV

Seventy-two patients who received VA-ECMO following cardiac arrest with CPR duration ≥1 minute during the study period were included in **Study IV**. **Table 13** presents a comparison between the baseline characteristics before VA-ECMO (i.e. before cannulation) of survivors with those of non-survivors at 90 days after initiation of support. Survivors and non-survivors differed significantly in IHD prevalence, initial cardiac arrest rhythm, low-flow duration, ROSC, median MAP, arterial pH and lactate just before cannulation. All cardiac arrests were witnessed by health care professionals on site with almost direct initiation of resuscitation, resulting in close to zero no-flow durations. Forty-six patients (64%) received VA-ECMO during ongoing CPR (absence of ROSC). The remaining 26 patients (36%) were initially successfully resuscitated to sustained ROSC after median 10 minutes (IQR: 2-17). Patients with sustained ROSC subsequently deteriorated secondary to refractory postarrest cardiogenic shock and VA-ECMO was initiated as the only remaining life-saving therapy. Sixty patients (83%) were cannulated by a femoral venoarterial (96%) or femoral artery-internal jugular vein access (4%).

TABLE 13. Comparison of pre-VA-ECMO characteristics between survivors and non-survivors at 90 days after VA-ECMO initiation

Pre-VA-ECMO characteristics	**MD (%)**	**All patients (n = 72)**	**Survivors (n = 31)**	**Non-survivors (n = 41)**	***P* value**
Male gender	0	54 (75)	23 (43)	31 (57)	0.891
Age (y)	0	56 (43-65; 11-76)	50 (36-62; 17-76)	59 (50-66; 11-76)	0.065
≥65 (y)	0	16 (22)	5 (31)	11 (69)	0.280
Weight (kg)	0	80 (73-90; 39-114)	78 (67-90; 51-102)	81 (75-90; 39-114)	0.308
BMI (kg/m^2)	0	25.9 (23.6-28.3)	24.7 (23.1-27.8)	26.6 (24.1-29.2)	0.098
Clinical presentation					
Ischemic heart disease	0	47 (65)	16 (34)	31 (66)	**0.034**
AMI	0	32 (44)	11 (34)	21 (66)	0.183
STEMI	0	31 (43)	11 (35)	20 (65)	0.259
Smoking	0	31 (43)	13 (42)	18 (58)	0.867
Hypertension	0	30 (42)	12 (40)	18 (60)	0.658
Valvular heart disease	0	24 (33)	10 (42)	14 (58)	0.866
Dyslipidemia	0	18 (25)	5 (28)	13 (72)	0.131
Diabetes mellitus	0	13 (18)	4 (31)	9 (69)	0.323
Hypertrophic cardiomyopathy	0	6 (8.3)	1 (17)	5 (83)	0.227
Prior† myocardial infarction	0	9 (13)	3 (33)	6 (67)	0.723

Atrial fibrillation	0	7 (9.7)	1 (14)	6 (86)	0.227
Prior† PCI	0	7 (9.7)	2 (29)	5 (71)	0.691
Prior† cardiac surgery	0	6 (8.3)	2 (33)	4 (67)	0.693
Chronic renal failure	0	5 (6.9)	1 (20)	4 (80)	0.382
Intoxication	0	5 (6.9)	4 (80)	1 (20)	0.158
Primary graft failure after heart transplantation	0	4 (5.6)	2 (50)	2 (50)	1.000
Acute myocarditis	0	3 (9.7)	3 (100)	0 (0)	0.075
Acute pulmonary embolus	0	3 (4.2)	1 (33)	2 (67)	1.000
Endocarditis	0	3 (4.2)	2 (67)	1 (33)	0.574
Cardiac arrest location					
Out-of-hospital	0	9 (12)	5 (56)	4 (44)	-
In-hospital	0	63 (88)	26 (41)	37 (59)	0.485
Intensive care unit	0	22 (31)	9 (41)	13 (59)	0.807
Catherization laboratory	0	18 (25)	6 (33)	12 (67)	0.336
Ward	0	12 (17)	7 (58)	5 (42)	0.242
Operating room	0	11 (15)	4 (36)	7 (64)	0.626
Initial cardiac arrest rhythm					
Shockable rhythm	0	31 (43)	21 (68)	10 (32)	-
Non-shockable rhythm	0	41 (57)	10 (24)	31 (76)	**<0.001**
No-flow duration (min)	0	0 (0)	0 (0)	0 (0)	-
Low-flow duration (min)	0	21 (10-73; 1-197)	10 (2-45; 1-120)	32 (20-100; 1-197)	**<0.001**
ROSC	0	26 (36)	19 (73)	7 (27)	-
Time to ROSC (min)	0	10 (2-17; 1-48)	5 (2-10; 1-20)	20 (17-30; 15-48)	**<0.001**
Absence of ROSC*	0	46 (64)	12 (26)	34 (74)	**<0.001**
Time to cannulation (min)	0	49 (20-107; 1-197)	55 (20-87; 1-120)	47 (20-116; 1-197)	0.670
MAP (mmHg)‡	0	50 (40-59)	55 (45-53)	45 (40-53)	**0.001**
Arterial pH‡	0	7.10 (6.94-7.30; 6.55-7.57)	7.18 (7.06-7.34; 6.63-7.57)	7.04 (6.90-7.22; 6.55- 7.39)	**0.002**
Arterial lactate (mmol/L)‡	0	12.0 (5.2-17.0; 1.3-28.0)	8.0 (2.9-12.9; 1.3-20.0)	15.0 (10.6-19.0; 1.6-28.0)	**<0.001**
<10 (mmol/L)	0	28 (39)	19 (68)	9 (32)	-
10-20 (mmol/L)	0	36 (50)	12 (33)	24 (67)	-
>20 (mmol/L)	0	8 (11)	0 (0)	8 (100)	**0.001**
<17 (mmol/L)	0	51 (71)	28 (55)	23 (45)	-
≥17 (mmol/L)	0	21 (29)	3 (14)	18 (86)	**0.002**
Hemoglobin (g/L)‡	0	109 (90-131)	114 (90-131)	108 (90-128)	0.785
INR	6.9	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.4 (1.1-1.7)	0.589
Creatinine (µmol/L)	2.8	130 (96-170)	133 (81-179)	124 (108-167)	0.887

GFR MDRD (mL/min/1.73m^2)	2.8	50 (38-71)	49 (40-77)	53 (35-66)	0.943
ALT (µkat/L)	14	2.13 (0.91-6.92)	1.71 (0.91-5.50)	2.53 (0.97-12.59)	0.401
Pre-VA-ECMO interventions					
Acute coronary angiography	0	42 (58)	16 (38)	26 (62)	0.315
Acute PCI	0	28 (39)	11 (39)	17 (61)	0.606
Cardiac surgery	0	31 (43)	12 (39)	19 (61)	0.571
Hemodialysis	0	9 (13)	3 (33)	6 (67)	0.723
No. of inotropes and vasopressors‡§	0	2 (2-3)	2 (1-3)	3 (2-3)	0.073
Intra-aortic balloon pump	0	8 (11)	3 (37)	5 (63)	1.000
Retrieval from external hospital	0	29 (40)	14 (48)	15 (52)	0.463
VA-ECMO insertion period¶					
2011-2015	0	36 (50)	15 (42)	21 (58)	-
2006-2010	0	36 (50)	16 (44)	20 (56)	0.812

Bold indicates statistical significance. Categorical variables are presented as numbers (n) and percentages (%), and compared with the Chi-square, Likelihood ratio or Fischer's exact test. Continuous variables are presented as median (interquartile range (IQR); range) and compared with the Mann-Whitney *U* test. *ALT*, alanine aminotransferase; *AMI*, acute myocardial infarction; *BMI*, body mass index; *GFR MDRD*, glomerular filtration rate modification of diet in renal disease; *INR*, international normalized ratio; *MAP*, mean arterial pressure; *MD*, missing data; *PCI*, percutaneous coronary intervention; *ROSC*, return of spontaneous circulation; *STEMI*, ST-elevation myocardial infarction; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation. †Prior to current medical event/admission. *Continuous chest compressions at cannulation. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan. ¶Postimplant variable only for descriptive purposes.

The following variables were found to be significantly associated with 90-day mortality in the univariable logistic regression analysis: IHD, initial non-shockable rhythm, absence of ROSC, low-flow duration, MAP, arterial pH and lactate (**Table 14A**).

TABLE 14A. Factors associated with mortality at 90 days after VA-ECMO initiation

		Univariable logistic regression			**Multivariable logistic regression**		
Variables	**MD (%)**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Male gender	0	1.08	0.37-3.16	0.891	-	-	-
Age (y)	0	1.03	1.00-1.06	0.079	-	-	-
≥65 vs. <65 (y)	0	1.91	0.59-6.21	0.284	-	-	-
Weight (kg)	0	1.02	0.98-1.05	0.364	-	-	-
BMI (kg/m^2)	0	1.13	0.98-1.30	0.107	-	-	-
Clinical presentation							
Ischemic heart disease	0	2.91	1.07-7.92	**0.037**	7.39	1.57-34.7	**0.011**
AMI	0	1.91	0.73-4.97	0.186	-	-	-

Smoking	0	1.08	0.42-2.78	0.867	-	-	-
Hypertension	0	1.24	0.48-3.20	0.658	-	-	-
Valvular heart disease	0	1.09	0.40-2.94	0.866	-	-	-
Dyslipidemia	0	2.41	0.76-7.71	0.137	-	-	-
Diabetes mellitus	0	1.90	0.53-6.86	0.328	-	-	-
Prior† myocardial infarction	0	1.60	0.37-6.98	0.532	-	-	-
Atrial fibrillation	0	5.14	0.59-45.2	0.140	-	-	-
Prior† PCI	0	2.01	0.36-11.2	0.423	-	-	-
Prior†cardiac surgery	0	1.57	0.27-9.16	0.618	-	-	-
Chronic renal failure	0	3.24	0.34-30.6	0.304	-	-	-
Intoxication	0	0.17	0.02-1.59	0.120	-	-	-
Primary graft failure after heart transplantation	0	0.74	0.10-5.59	0.774	-	-	-
Acute myocarditis	0	0.36	0.03-4.19	0.416	-	-	-
Acute pulmonary embolus	0	1.54	0.13-17.8	0.730	-	-	-
Endocarditis	0	0.36	0.03-4.19	0.416	-	-	-
Cardiac arrest location							
In-hospital	0	1.78	0.44-7.27	0.422	-	-	-
Catherization laboratory	0	1.72	0.57-5.27	0.339	-	-	-
Operating room	0	1.39	0.37-5.25	0.627	-	-	-
Intensive care unit	0	1.14	0.41-3.14	0.807	-	-	-
Ward	0	0.48	0.14-1.68	0.248	-	-	-
Out-of-hospital	0	0.56	0.14-2.30	0.422	-	-	-
Initial cardiac rhythm							
Shockable rhythm	0	0.15	0.05-0.43	**<0.001**	-	-	-
Non-shockable rhythm	0	6.51	2.31-18.7	**<0.001**	12.2	2.83-52.7	**0.001**
Absence of ROSC*	0	7.69	2.59-22.8	**<0.001**	2.46	0.51-11.9	0.262
Low-flow duration (min)	0	1.02	1.01-1.03	**0.008**	1.01	0.99-1.03	0.398
MAP (mmHg)‡	0	0.92	0.88-0.97	**0.002**	-	-	-
Arterial pH‡	0	0.03	0.00-0.31	**0.004**	-	-	-
Arterial lactate (mmol/L)‡	0	1.17	1.07-1.27	**<0.001**	1.15	1.01-1.31	**0.041**
Hemoglobin (g/L)‡	0	1.00	0.98-1.02	0.983	-	-	-
INR	6.9	1.00	0.53-1.90	1.000	-	-	-
Creatinine (µmol/L)	2.8	1.00	0.99-1.01	0.693	-	-	-
GFR MDRD (mL/min/1.73m^2)	2.8	1.00	0.99-1.01	1.000	-	-	-
ALT (µkat/L)	14	1.02	0.98-1.01	0.373	-	-	-
Pre-VA-ECMO interventions							
Acute coronary angiography	0	1.63	0.63-4.20	0.316	-	-	-

Acute PCI	0	1.29	0.49-3.37	0.607	-	-	-
Cardiac surgery	0	1.34	0.53-3.53	0.518	-	-	-
Hemodialysis	0	1.60	0.37-6.98	0.532	-	-	-
Intra-aortic balloon pump	0	1.30	0.29-5.89	0.737	-	-	-
No. of inotropes and vasopressors‡§	0	1.52	0.93-2.50	0.098	-	-	-
Retrieval from external hospital	0	0.70	0.27-1.81	0.463	-	-	-

Bold indicates statistical significance. *ALT*, alanine aminotransferase; *AMI*, acute myocardial infarction, *BMI*, body mass index; *CI*, confidence interval; *GFR MDRD*, glomerular filtration rate modification of diet in renal disease; *INR*, international normalized ratio; *MAP*, mean arterial pressure; *MD*, missing data; *OR*, odds ratio; *PCI*, percutaneous coronary intervention; ROSC, return of spontaneous circulation; *STEMI*, ST-elevation myocardial infarction; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation.†Prior to current medical event/admission. *Continuous chest compressions at cannulation. ‡Just before cannulation. §Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, milrinone, levosimendan.

MAP and pH were excluded from the model due to high collinearity with lactate. pH but not lactate was excluded as the latter variable can be considered a more robust variable and less sensitive to administration of buffer solutions during CPR and the influence of PaCO2. Non-linearity did not impact the logistic regression analysis according to the restricted cubic splines analysis, supporting the use of the model.

Three independent factors made significant contributions to the model in the multivariable logistic regression analysis (**Table 14B**). Non-shockable rhythm as initial presenting cardiac arrest rhythm was the most significant predictor followed by presence of IHD and arterial lactate level.

TABLE 14B. Factors associated with mortality at 90 days after VA-ECMO initiation

		Univariable logistic regression			**Multivariable logistic regression**		
Variables	**MD (%)**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Ischemic heart disease	0	2.91	1.07-7.92	**0.037**	7.39	1.57-34.7	**0.011**
Non-shockable rhythm	0	6.51	2.31-18.7	**<0.001**	12.2	2.83-52.7	**0.001**
Absence of ROSC*‡	0	7.69	2.59-22.8	**<0.001**	2.46	0.51-11.9	0.262
Low-flow duration (min)	0	1.02	1.01-1.03	**0.008**	1.01	0.99-1.03	0.398
MAP (mmHg)‡	0	0.92	0.88-0.97	**0.002**	-	-	-
Arterial pH‡	0	0.03	0.00-0.31	**0.004**	-	-	-
Arterial lactate (mmol/L)‡	0	1.17	1.07-1.27	**<0.001**	1.15	1.01-1.31	**0.041**

Bold indicates statistical significance. *CI*, confidence interval; *MAP*, mean arterial pressure; *MD*, missing data; *MAP*, mean arterial pressure; *MD*, missing data; *OR*, odds ratio; *ROSC*, return of spontaneous circulation; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation. *Continuous chest compressions at cannulation. ‡Just before cannulation.

The full model with the independent predictors, was statistical significant, χ^2 (df = 5, n = 72) = 41.765; p <0.001. Thus, the model was able to discriminate between survivors and non-survivors at 90-days. The χ^2 for Hosmer-Lemeshow's Test was 7.619 with a significance level of p = 0.47, which further supports the use of our model. The model as a whole explained between 44% (Cox and Snell R^2) and 59% (Nagelkerke R^2) of the variance of the 90-day mortality and overall correctly classified 83% of the cases. The sensitivity and specificity of the model was 85% and 81%, respectively, giving a positive predictive value of 85% and a negative predictive value of 81%.

The Kaplan-Meier survival curves until 90 days after VA-ECMO initiation are presented in **Figure 10** and indicate significant worse outcome for (A) lactate level ≥17mmol/L (153mg/dL) (90% specificity), and (B) non-shockable compared with shockable rhythm. All patients (8 of 8) with a lactate level >20mmol (180mg/dL) died within 6 days.

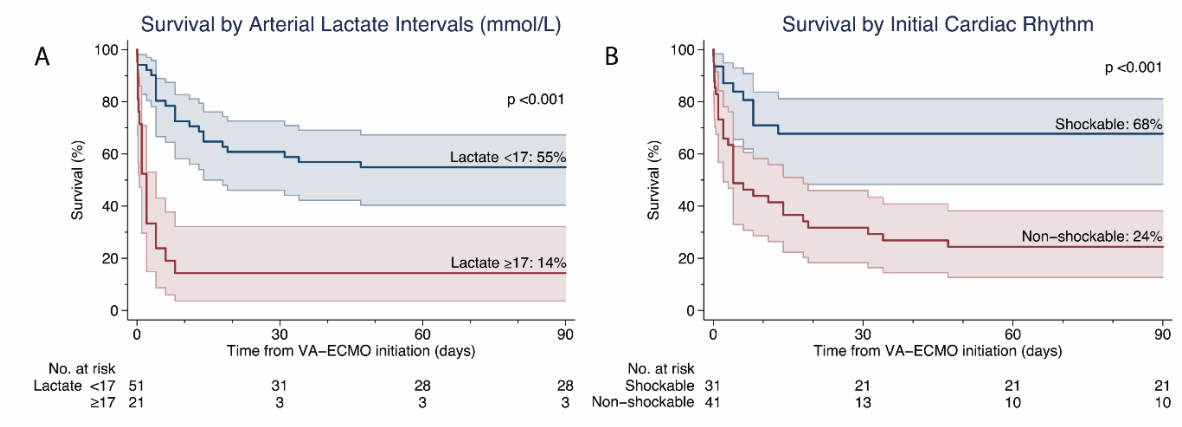

FIGURE 10. Kaplan-Meier survival curves until 90 days after initiation of VA-ECMO support related to **(A)** arterial lactate intervals at initiation of VA-ECMO, and **(B)** initial cardiac arrest rhythm, with 95% confidence intervals, in 72 patients with cardiac arrest. *VA-ECMO*, venoarterial extracorporeal membrane oxygenation.

The all-cause mortality at 90 days, which was the primary endpoint, was 57% (n = 41). Within 72 hours 19 patients (26%) died and within the first week after VA-ECMO onset 28 patients (39%) succumbed. During VA-ECMO 38 patients (53%) died. The in-hospital mortality was 57% (n = 41) and 43% (n = 31) were discharged home, all with a good neurological outcome defined as CPC score 1-2 as presented in **Table 15**. The main causes of death during VA-ECMO were brain injuries and multiorgan failure, 21% (n=15) respectively, and within 90 days anoxic brain injury 22% (n=16) (**Table 15**).

TABLE 15. Outcomes

Variables	MD (%)	All patients (n = 72)
VA-ECMO duration (days)	0	5 (2-12; 1-55)
VA-ECMO destination		
Death during VA-ECMO	0	38 (53)
Successful weaning*	0	31 (43)
VA-ECMO to heart transplantation	0	3 (4.2)
VA-ECMO to LVAD	0	0 (0)
Mortality within		
24 hours	0	13 (18)
48 hours	0	17 (24)
72 hours	0	19 (26)
7 days	0	28 (39)
30 days	0	38 (53)
90-day mortality	0	41 (57)
In-hospital mortality	0	41 (57)
Discharge to home	0	31 (43)
Days from VA-ECMO initiation to discharge home	0	51 (29-101; 13-295)
CPC score at discharge to home	0	31 (43)
CPC 1-2	0	31 (100)
CPC 3-4	0	0 (0)
Cause of death during VA-ECMO	0	38 (53)
Cerebral†	0	15 (21)
Multiorgan failure	0	15 (21)
Cardiac‡	0	4 (5.5)
Bleeding§	0	3 (4.2)
Miscellaneous¶	0	1 (1.4)
Cause of death within 90 days	0	41 (57)
Cerebral†	0	16 (22)
Multiorgan failure	0	15 (21)
Cardiac‡	0	4 (5.5)
Bleeding§	0	3 (4.2)
Miscellaneous¶¥	0	3 (4.2)

Categorical and continuous variables are presented as numbers (n), percentages (%), and median (interquartile range (IQR); range), respectively. *CPC*, cerebral performance category; *LVAD*, left ventricular assist device; *MD*, missing data; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation. *Survival >48 hours after weaning/without re-initiation of VA-ECMO. †Fatal anoxia, brain death, stroke. ‡Sudden cardiac arrest, myocardial infarction, heart failure. §Lung, gastrointestinal, retroperitoneal. ¶Iatrogenic air entry into VA-ECMO-circuit (n = 1). ¥Pulmonary embolus and ischemic colitis (n = 1), pulmonary embolus (n = 1).

Figure 11 depicts the most frequent complications after initiation of VA-ECMO being renal failure necessitating hemodialysis (54%) followed by pneumonia (43%) and anoxic brain injuries (19%).

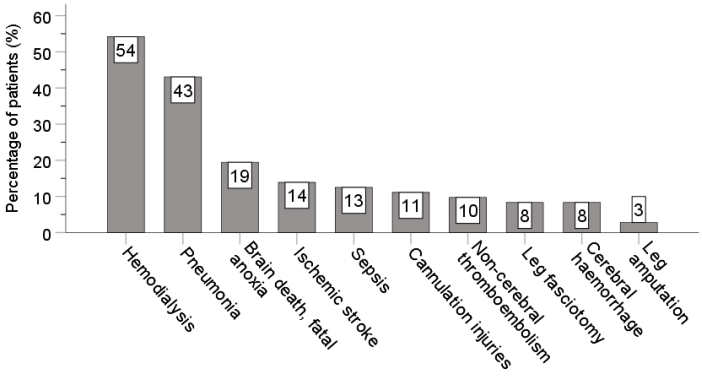

FIGURE 11. Main complications after initiation of venoarterial extracorporeal membrane oxygenation in 72 patients with cardiac arrest.

5 DISCUSSION

The major findings in this thesis were as follows.

In an unselected population with refractory cardiogenic shock three independent pre-VA-ECMO predictors for 90-day mortality were identified; arterial lactate level, number of inotropes and vasopressors, and presence of IHD, which all demonstrated an explicit fall in survival during the first 20 days, after which they leveled out until 90 days after VA-ECMO initiation. The 90-day mortality rate corresponded to the in-hospital mortality rate both reaching 54% (**Study I**).

In patients with refractory postcardiotomy cardiogenic shock two independent pre-VA-ECMO predictors for 90-day mortality in patients with refractory postcardiotomy cardiogenic shock; arterial lactate level and IHD. Moreover, the 90-day morality rate was 57% and the in-hospital mortality rates was 56%. The presented in-hospital mortality rate was one of the lowest rates reported in unselected refractory postcardiotomy patients (**Study II**).

In an unselected non-surgical population with refractory cardiogenic shock supported by VA-ECMO two independent pre-VA-ECMO predictors for 90-day mortality were identified; arterial lactate and number of vasopressors and inotropes just before cannulation (**Study III**).

In an unselected population with cardiac arrest prior to VA-ECMO three independent predictors for mortality were identified; initial non-shockable rhythm, presence of IHD, and arterial lactate, as independent pre-VA-ECMO predictors for 90-day mortality in patients with cardiac arrest prior to VA-ECMO, whereas low-flow duration, ROSC and age were not significant (**Study IV**).

5.1 PRIMARY ENDPOINT

The primary endpoint mortality within 90-days after initiation of VA-ECMO was chosen throughout the thesis over 30-day mortality, as in **Study I** 7.2% (13 of 181 patients), **Study II** 6.7% (7 of 105 patients), **Study III** 7.9% (6 of 76 patients) and **Study IV** 5.6% (4 of 72 patients) of patients had VA-ECMO support ≥30 days (up to 55 days). Furthermore, the Kaplan-Meier survival curves flattened out before reaching 90 days, which indicated that it would be of limited additional value to extend to follow-up beyond 90 days regarding identification of pre-implant outcome predictors. In addition, the outcome variable 90-day mortality was used as the also commonly used alternative, alive at hospital discharge, does not

include a specific time span. Even though patients may survive 90 days after VA-ECMO implantation, individual patients may still be hospitalized. Therefore, the variable discharge to home in was added as exemplified by the fact that 13% of patients (23 of 181) had a longer hospital stay than 90 days (up to 295 days).

Cause of death after discharge was not chosen as an outcome variable in the thesis as it is dependent on follow up time, patient age, life style and comorbidity with different life expectancy. As follow up time increases other factors independent of etiology for VA-ECMO support will become more important as cause of mortality. Studies within the field have therefore, besides alive at hospital discharge, focused on specific time intervals after VA-ECMO initiation preferably reporting 30-, 90-day, 1-year mortality vs. survival rates rather than an unspecific time point for outcome as "after discharge" which therefore is not presented in **Study I-IV**.

5.2 OUTCOME PREDICTORS

This thesis identified pre-VA-ECMO predictors for 90-day mortality in an undifferentiated population of refractory cardiogenic shock patients (**Study I**), as well as in specific subgroups defined in **Study II-IV**.

5.2.1 Arterial lactate

Lactate is a metabolic end product of anaerobic glycolysis and is considered to be indicator of tissue perfusion, which is affected by both macro- and microcirculation. The worse the tissue hypoperfusion is the higher the lactate and risk for mortality.[46, 70-73] In refractory cardiogenic shock the arterial lactate level is a marker of general tissue hypoperfusion, following low cardiac output with impaired tissue oxygenation and anaerobe metabolism.[72, 73] Regarding physiology and lactate behavior, cardiogenic shock with tissue hypoperfusion, has several pathophysiological consequences including imbalance between oxygen delivery and consumption, global tissue hypoxia, and anaerobic metabolism under the simultaneous influence of catecholamines. The resulting behavior of lactate, including its clearance, as being the provider of "rescue energy" is a complex topic and was not the aim of this thesis. However, lactate physiology in critical illness including cardiogenic shock and after cardiac surgery has been described in detail elsewhere.[70, 74-80] Metabolic acidosis will be treated with intravenous buffer solutions, including sodium bicarbonate, which will influence base excess and arterial

pH but not arterial lactate. Thus, in **Study I-IV** arterial lactate levels was focused upon and not base excess levels.

The importance of arterial lactate in the setting of cardiogenic shock and indication for VA-ECMO support has been previously discussed by other groups. With a similar study population size, 179 compared to 181 patients in **Study I**, Truby et al.,[39] only found etiology of refractory cardiogenic shock as a significant pre-VA-ECMO predictor for in-hospital mortality (61%). However, several of their variables had a large proportion of missing data, including arterial lactate (34%). Remarkably, the median arterial lactate level in their study cohort was 5.45 mg/dL (IQR: 2.7-9.3) corresponding to 0.6 mmol/L (IQR: 0.3-1.0), which should be compared with a median of 7.1 mmol/L (IQR: 3.1-14.0) in **Study I** (**Table 3)**. Most likely, this is explained by a selection bias, where arterial lactate sampling was collected from only relatively stable patients and not from patients rapidly deteriorating due to refractory cardiogenic shock with a more pronounced oxygen delivery deficit. This illustrates the weakness of studies with incomplete data, where a high proportion of missing data not missing at random may lead to internally and externally unreliable results. In contrast, all variables included in the multivariable logistic regression analysis were complete and thus arterial lactate, a marker of severe hypoperfusion, became a highly significant independent predictor of 90-day mortality (**Table 4A, B)**. Arterial lactate has in agreement with **Study I** also been found to be an independent pre-VA-ECMO predictor of short and midterm survival in several other single center studies with unselected patients' populations.[40, 42, 43, 64, 67, 81] In **Study I-IV**, it was possible to identify specific lactate intervals where increasing levels of lactate indicated worse survival as presented in the Kaplan-Mayer survival curves (**Figure 3A, 5A, 8, 10A**).

In **Study II,** evaluating refractory postcardiotomy cardiogenic shock patients, lactate was identified to have an OR of 1.22 per mmol/L, again implying progressively worse outcomes with increasing lactate levels. High lactate levels at the end of cardiac surgery due to an imbalance between oxygen delivery and requirement resulting in tissue hypoxia and organ failure has previously been identified as an independent predictor of negative outcome after cardiac surgery.[76, 78, 80] Regarding the lactate cut off level of 10 in **Study II** (**Figure 5A**) and the survival ROC, a clear postoperative cut-off value for lactate has previously not been identified and values consequently differ between studies. A survival ROC analysis of lactate identified a value of 5.8mmol/L, corresponding to a sensitivity of 75.0% and specificity of 40.0%. However, despite this value being statistically correct it is not a clinically relevant "cut off" value to be applied in an VA-ECMO practice, where the likelihood of death in the absence of VA-ECMO is deemed to be extremely high i.e. a significant part of patients will also die

with lower lactate levels. Instead, lactate was identified as an independent predictor for 90-day mortality with an OR of 1.22 per mmol/L, implying progressively worse outcomes with increasing lactate levels. Based on our daily practice we divided the study population into four chosen subgroups of lactate with arbitrary cut off levels of <5, 5-9.9, 10-14.9, ≥15mmol/L (**Table 7**) to facilitate clinical interpretation of lactate as a strong and significant predictor. However, postulating cut off levels whether statistically calculated or arbitrary chosen entail a risk that these cut off levels will be clinically perceived as cut off levels to either offer or to exclude patients from VA-ECMO support. This is part of a larger discussion, which was not the aim of this thesis to elucidate. However, in such a discussion the concept of optimization of sensitivity and specificity according to ROC analysis has to be addressed. There is an obvious risk to overemphasize the importance of a high sensitivity to identify patients (the true positives) who died in this setting. Increasing sensitivity will lower the lactate cut off to very low levels, as also patients died with normal lactate levels. Consequently, a significant part of the patients with high lactate levels also survived. Therefore, in accordance to other clinical centers, specificity can be considered to be more important to focus upon when to facilitate clinical interpretation of lactate on outcome. Thus, it is more important to identify patients who will not die (the true negatives). Besides dividing the study population into the four above mentioned lactate groups to facilitate interpretation of the importance on the increasing levels of lactate on outcome, it was additionally chosen to present a more simplified and clinically applicable figure (**Figure 5A**) with 10 as an arbitrary cut off level, as a single cut off level is easier to refer to than four different cut off subgroups. The cut off level of 10 was chosen as it corresponds to a specificity of 91% (ROC survival of 9%) implying that at a lactate level of 10 identified >90% of the patients that died in the population. To rise the cut off to 15mmol/L would have identified 100% of non-survivors and at the same time raised the question if VA-ECMO out of ethical reasons should be offered to patients with near to or 100% expected mortality (same single cut off approach was chosen in **Study IV, Table 10A**).

Moreover, the identification of arterial lactate as an independent pre-VA-ECMO predictor of mortality after cardiac surgery complies with the two studies of Park et al.[46, 71] on 115 and 93 patients, respectively, where blood lactate before initiation of VA-ECMO) was as an independent predictor of in-hospital mortality (OR: per unit lactate, 1.19 and 1.13, respectively). Likewise, Papadopoulos et al.[45] discovered that a pre-VA-ECMO serum lactate level of >120mg/dL (>13.3mmol/L) significantly worsened in-hospital survival in 360 postcardiotomy cardiogenic shock patients (OR: 2.6) as did Rastan et al.,[44] who identified that a lactate level of >4mmol/L in the operating room, and >10 mmol/L immediately after VA-ECMO initiation in 517 refractory postcardiotomy cardiogenic shock patients, were significant

predictors of in-hospital mortality (OR: 2.21 and 2.65, respectively). Additionally, an important feature that strengthens the impact of arterial lactate as a predictor was that we in **Study II** identified that increasing intervals of arterial lactate corresponded with progressively worse survival (**Table 7** and **Figure 5A**), which to our knowledge is the first time to be reported in refractory postcardiotomy cardiogenic shock in a pre-VA-ECMO setting.

Arterial lactate remained an independent pre-VA-ECMO predictor of 90-day mortality in **Study III (Table 11A, B)**, evaluating non-surgical refractory cardiogenic shock, which is agreement with several other studies with selected or unselected non-surgical populations.[40, 61, 67]

Finally, in **Study IV**, lactate level was also found to be predictive of 90-day mortality in the pre-VA-ECMO cardiac arrest setting, which is only supported by a limited number of previous cardiac arrest studies,[82-86] presumably explained by missing lactate data in the majority of these studies. In conventional CPR, lactate levels have previously been identified as a survival and neurological prognostic marker.[87] In cardiac arrest or refractory postarrest cardiogenic shock, arterial lactate is as previously discussed indicative of the magnitude of anaerobic metabolism following systemic hypoperfusion and tissue hypoxia and consequently epitomizes a surrogate marker of "no and low-flow duration" with insufficient tissue perfusion resulting in end-organ failure.[87-90] In **Study IV**, a lactate cut off level of ≥17mmol/L was identified (**Table 13** and **Figure 10A**) to correspond with a specificity of 90% (10% ROC survival), in accordance to the previous considerations on specificity and sensitivity discussed above. A lactate cut off level of 20mmol/L would have identified 100% of non-survivors and at the same time raised the question if VA-ECMO out of ethical reasons should be offered to patients with a near to or 100% expected mortality. Using the 20mmol/L criterion, 8 of 72 patients (11%) in **Study IV** should not have been cannulated. Similarly, Megarbane et al.[91] in a study including 66 extracorporeal CPR (ECPR) patients found that a pre-VA-ECMO lactate level ≥21mmol/L was associated with 100% mortality. However, it must be kept in mind that lactate levels can reach extreme values before cannulation and still be associated with survival in poisoning-related refractory cardiac arrest.[92]

5.2.2 Inotropes and vasopressors

Administration of intravenous inotropes and vasopressors,[20, 93] often in combination, is the pharmacological approach to initially counteract refractory cardiogenic shock. Intravenous inotropes and vasopressors have in this context been identified to be a significant independent

predictor of 90-day mortality, which is supported by previous studies indicating that the extent of vasoactive support predicts outcome in various ECMO and non-ECMO settings.[45, 53, 94-96]

The amount of intravenous inotropic and vasopressor support was in **Study I-IV** graded into the simple and clinically relevant "number" of ongoing drugs just before cannulation for VA-ECMO. The time (number infusion hours) or mean drug doses of vasoactive agents before VA-ECMO was deliberately not studied, though previously described,[94, 97] being a challenging variable to interpret and even more complex when the aim is to facilitate a clinically applicable and rapid approach to predict risk were pharmacological support is included. A number-of-hours-analysis would also have to address interchanging doses and combinations of drugs with separate pharmacokinetics. This would involve different number of hours per drug in combination with the simultaneously ongoing volume loading in patients, who are often rapidly deteriorating hemodynamically within the last hours before cannulation. Moreover, to calculate the mean doses of the specific drugs during an arbitrary number of pre-VA-ECMO hours is challenging as patients with refractory cardiogenic shock are on a slippery sliding slope, which will misallocate interpretation of mean doses in relation to time of cannulation as initially lower upstart doses with fewer drugs several hours or days earlier will mask higher doses closer to cannulation. To overcome the complicated calculation and interpretation of the impact of pharmacological support on outcome, we applied a simpler and clinically more applicable method to facilitate evaluation and risk prediction by counting the number of drugs, which were considered to have a pharmacological effect in the patient last before cannulation regardless of overall mean dose or number of hours.

One may argue that behind use of escalating doses of vasoactive drugs and increasing lactate levels is a decrease in the cardiac output. Therefore, adequate hemodynamic assessment including cardiac output/ index values before initiation of VA-ECMO in the two groups (survivors/ non-survivors) could be considered to determine if this is true. Furthermore, in the absence of such a measurement, the use of vasoactive drugs could have led to more tissue ischemia and increasing lactate levels. However, monitoring cardiac output/cardiac index (CO/CI) before initiation of VA-ECMO was not the primarily applicable diagnostic approach in our setting with an undifferentiated refractory cardiogenic shock population threatened with impending death, where 49% (51 of 105) of the patients undergoing cardiac surgery (**Study II**) were not able to be separated from perioperative CPB, and thus accordingly were cannulated in the OR (**Table 7 and 8A**). Furthermore, in **Study I,** 40% of the patients underwent CPR within 12 hours before cannulation, 25% (46 of 181) under ongoing heart compressions, and 7% and 35% of the patients were cannulated in the catheter laboratory and

or retrieved from external hospitals general intensive care units (often without specific CO/CI monitoring), respectively. Evidently, the majority of our patients were not slowly deteriorating after or during a complete hemodynamic investigation or monitoring, but rapidly deteriorating. Insertion of a complimentary pulmonary artery catheter for measuring of CO/CI beyond the rapid information given by echocardiography, the patient's clinical and metabolic state, and the level of other ongoing support, were not considered being sufficiently valuable in bringing further information crucial on deciding on the suitability of cannulation. More so, this would have risked delaying implantation of VA-ECMO in these extremely hemodynamically unstable and critically ill patients. Consequently, CO/CI was only registered in 24% of the patients before initiation of VA-ECMO.

To our knowledge, **Study I and III** are the first studies to present that the number of inotropes and vasopressors at initiation of VA-ECMO independently predicts survival at 90-days in adults with refractory cardiogenic shock.

5.2.3 Ischemic heart disease

In **Study I** and **II**, IHD, was the only organ specific predictor. This is supported by previous studies where IHD in general is associated with worse outcomes compared with non-IHD.[2, 98]

Evidently, all patients in **Study II** who underwent elective CABG had IHD. These two factors were significant in the multivariable analysis, but highly correlated in the multicollinearity analysis. Furthermore, not all patients with IHD underwent CABG unless presence of significant and graftable stenosis, whereby IHD had a higher prevalence than CABG. Thus, IHD was kept and CABG excluded from the model. Moreover, IHD correlated significantly with AMI, wherefore AMI also was removed from the model.

In the non-surgical VA-ECMO population (**Study III**) neither AMI, IHD or other non-surgical etiologies were identified as independent predictors of 90-day mortality. Despite AMI being the most frequent reason for CS in other studies, [3, 4, 99] we were not able to identify AMI per se as an independent predictor of 90-day mortality in with refractory cardiogenic shock, even though cardiovascular disease generally is associated with worse expected outcome. [63, 98] It must therefore be recognized that neither AMI per se nor the cohort of other non-surgical etiologies were significantly associated with mortality after initiation of VA-ECMO, which agrees with the recently published single center study by Waha et al. [32] Thus, the severity of cardiogenic shock indicated as the levels of lactate and number of vasoactive agents discussed above just before start of VA-ECMO may be more predictive of outcome than the specific etiology of cardiogenic shock.

The significance of IHD as a pre-implant predictor of 90-day mortality after VA-ECMO initiation was further verified by its identification in **Study IV**. This finding is supported by previous studies indicating poor outcome in patients with IHD undergoing cardiac arrest and that sudden cardiac death, being the worldwide leading cause of all deaths, occurs in the majority in patients with atherosclerotic coronary artery disease (65–85%).[100, 101]

5.2.4 Non-shockable rhythm

There are no universal time criteria to define refractory cardiac arrest. Most studies have arbitrary excluded patients with low-flow durations (i.e. CPR duration) below 10-30 minutes. In contrast, we included patients with low-flow durations down to 1 minute (median 21 minutes, IQR: 10-73), to evaluate the influence of the time component low-flow duration on outcome. This permitted us to analyze the complete range of low-flow durations with other factors, including lactate, without excluding patients with arbitrary short low-flow durations. The finding in **Study IV** that initial non-shockable rhythm was an independent predictor of mortality after VA-ECMO initiation (**Table 14A, B**) is in agreement with several other studies.[9, 84, 102-106] Conversely, Dennis et al.[85] failed to find such an association, most probably due to a type II error with only 3 out of 37 included patients with asystole (i.e. non-shockable rhythm).

Indeed, in the univariable logistic regression analysis low-flow duration and absence of ROSC were identified as significant predictors for 90-day mortality after VA-ECMO initiation. However, both factors lost their significance in the multivariable analysis ($p = 0.398$ and $p = 0.262$, respectively) in contrast to the factors non-shockable rhythm, lactate and IHD. Several studies have reported low-flow duration to be an independent predictor of outcome,[102-104, 107, 108] but in contrast to **Study IV**, those studies did not include lactate in the analyses. This may further support that arterial lactate represent a metabolic marker superior to the precarious factor low-flow duration, which is influenced by CPR quality, the often-inexact no and low-flow time estimations, and the possibility of undetected interim periods of ROSC during ongoing CPR. Thus, the metabolic state, expressed as level of lactate just before start of VA-ECMO, seems to be more predictive of outcome than low-flow time (i.e. CPR duration) or absence of ROSC. The latter further supports that lactate should be obtained from patients during and after CPR when VA-ECMO is considered as salvage therapy.

5.3 SELECTION OF VA-ECMO CANDIDATES

VA-ECMO for refractory cardiogenic shock is a highly resource demanding therapy with potential life-threatening complications. Additionally, even if VA-ECMO support is instituted as salvage therapy for refractory cardiogenic shock, mortality remains high. Therefore, optimal selection of suitable candidates and timing of implantation are crucial. Consequently, it is important to identify independent pre-VA-ECMO predictors on mortality without simultaneously including on-VA-ECMO variables in the outcome analysis. Only a limited number of studies have specifically addressed pre-VA-ECMO factors for risk prediction in an undifferentiated population with refractory cardiogenic shock.[14, 39, 64] In addition, earlier larger studies have often reported a combination of non-surgical and surgical patients,[14, 35, 39, 53, 63, 64] not presented rate of missing or considerably incomplete data,[14, 32, 33, 40, 61, 66] or as discussed above, included both variables before and during VA-ECMO.[65, 66]

The multicenter study by Schmidt et al.,[14] including 3846 patients with refractory cardiogenic shock receiving VA-ECMO from 280 centers (patients who received VA-ECMO during CPR were excluded from their analysis) demonstrated a hospital mortality rate of 58%, compared with 54% in **Study I**, which included patients receiving VA-ECMO during CPR. Schmidt et al.[14] identified 11 factors, including age, weight, chronic renal failure, time on mechanical ventilation before initiation of VA-ECMO, extra-cardiac organ failures, cardiac arrest, congenital heart disease, cause of cardiogenic shock, hemodynamic state, serum bicarbonate value, and peak inspiratory pressure, to be pre-VA-ECMO predictors of in-hospital mortality. However, in multicenter based registries the proportion of missing data has to be considered and in the study by Schmidt et al. only 23% of the patients had complete data.[14] Moreover, a single center study like **Study I** avoided the inherent intercenter variability of practice habits, patient selection and data reporting, which results in heterogeneity when pooled analyses are performed. In contrast, almost all variables included in our analysis had complete data and no patients were lost during follow up.

It must also be recognized that in **Study I** differing etiologies of refractory cardiogenic shock created three distinct subgroups of patients within our overall cohort, each having differing expected outcomes as described in previous studies.[2, 14, 39, 81, 109, 110] However, **Study I** demonstrated that none of the three etiology cohorts significantly predicted 90-day mortality after initiation of VA-ECMO (**Table 4A**). Thus, the hemodynamic state during refractory cardiogenic shock, as indicated by lactate levels, level of pharmacological support and the presence of IHD, appeared to be more important than the specific cardiac etiology causing refractory cardiogenic shock.

Previous outcome studies in refractory postcardiotomy cardiogenic shock have also not addressed explicitly pre-VA-ECMO predictors for outcome, but rather combining preoperative, surgical, and on-VA-ECMO (i.e. during support) factors. However, inclusion of on-VA-ECMO factors (i.e. after cannulation) will evidently be problematic when the aim is to predict outcome before VA-ECMO is initiated (i.e. just before cannulation). In addition, to focus on exclusively pre- and intraoperative variables may only be appropriate in patients who cannot be weaned from CPB, i.e. bridged directly from CPB to VA-ECMO, as 11-65% of studied postcardiotomy cardiogenic shock patients were weaned from CPB and transported to the ICU before VA-ECMO initiation due to hemodynamic deterioration after a varying number of hours or days.[2, 8, 34, 44, 46, 49, 51]

Rastan et al.[44] included 517 patients with refractory postcardiotomy cardiogenic shock in the largest published single center study. Many preoperative, surgical, and on-VA-ECMO factors were included in the analysis, whereby several independent predictors for in-hospital mortality were identified. Merely, 40% of the patients were bridged directly to VA-ECMO from CPB. However, in patients weaned from CPB, factors that occurred between weaning from CPB and start of VA-ECMO were not included in the analysis by Rastan et al.[44] This approach omits the identification of particularly pre-VA-ECMO predictors in the majority (60%) of patients. Equally, Papadopoulos et al.[45] included 360 postcardiotomy cardiogenic shock patients in the second largest single center study in which 7 independent predictors for in-hospital mortality were identified, while type of cannulation, an on-VA-ECMO risk factor, was included in the risk factor analysis. In contrast, in **Study II** we included several complementary variables after surgery until start of VA-ECMO in the analysis in addition to preoperative and surgical factors. To our knowledge, **Study II** is the first study to specifically address identification of pre-VA-ECMO predictors for 90-day mortality in unselected patients with refractory postcardiotomy cardiogenic shock.

In **Study II** the in-hospital mortality rate was 56%, which to our knowledge is one of the lowest mortality rates in an undifferentiated cohort with refractory postcardiotomy cardiogenic shock population supported with VA-ECMO reported from a single center. In comparison, in-hospital mortality rates have been reported to be between 53.4 and 76.3% in earlier studies.[2, 44, 45, 53] The incidence of postcardiotomy VA-ECMO at our tertiary center was 1.3% of the patients undergoing cardiac surgery, which is in the midrange of other publications within the field (0.6-2.9%) and similar to the large publications by Doll et al., 1.2%[2] and Rastan et al., 1.3%.[44] Nevertheless, outcomes in refractory postcardiotomy cardiogenic shock supported by VA-ECMO are overall poor, which emphasizes identification of clinically usable predictors

to optimize prognostication and thereby selection of suitable candidates, who are considered to have a reasonable chance of survival by initiation of VA-ECMO.

In **Study II** 51% of the population was successfully weaned from VA-ECMO, in comparison to between 31% and 63.5% in earlier publications.[2, 44, 45, 55] Nevertheless, comparisons between studies are demanding due to unclear definitions on what can be considered to be successful weaning, i.e. survival time after weaning, and non-reporting of data.[8, 44] The percentage of patients discharged alive, without having been bridged to long term mechanical circulatory support (ventricular assist device [VAD]) heart transplantation, should be related to the reported percentage of successful weaning, regardless of having survived weaning with an arbitrary defined number of hours or days, besides comparing patient characteristics, weaning and bridging rates.

To estimate the proportion of patients who were excluded from VA-ECMO at our tertiary center because they were too sick would be to subtract the 2.5% 30-day mortality rate in all our patients undergoing cardiac surgery (during the study period), with the 0.7% mortality rate in the patients supported with VA-ECMO (1.3% of all our patients received VA-ECMO, and 51% of them died within 30 days: 1.3 x 0.51 = 0.7%). Thus, 2.5% - 0.7% = 1.8% of the patients were probably excluded from VA-ECMO because they were either too sick or died after discharge within 30 days after the operation.

Besides **Study III**, Waha et. al.[32] have published the large and only single center study that has focused on the impact of specifically pre-ECMO predictors of outcome in unselected patients with refractory cardiogenic shock receiving VA-ECMO without prior surgery. The study by Waha et. al. [32] had several similarities with **Study III**: the number of included patients' n = 83 vs. n = 76: proportion of males 74% vs. 74%, PCI in AMI patients 93% vs. 92%, pre-ECMO CPR 55% vs. 54%, VA-ECMO duration median 6 days vs. 5 days, and death during VA-ECMO 43% compared with 46% in **Study III**.

The lower in-hospital and 18-month mortality, 50.0% and 51.3% respectively, in **Study III**, compared with the data presented by Waha et al., 68.7% and 81.9% respectively, may partly be explained by an older study population (median age 9 years higher, all 14 patients >75 years died prior to hospital discharge) and a higher rate of AMI (64% vs. 51% in **Study III**). An unexpected and uncommented finding by Waha et al. was a higher pre-VA-ECMO lactate in survivors compared with non-survivors, which is in blatant disparity to the results in **Study III** and earlier studies on VA-ECMO treatment of non-surgical refractory cardiogenic shock.[35, 40, 61] This may possibly be explained by a selection bias, i.e. that arterial lactate

sampling was restricted to relatively circulatory stable patients and omitted in unstable refractory cardiogenic shock patients with a more manifest oxygen deficit (rate of missing data not presented). Thus, such a selection bias may be clarified by the non-random absence of complete data, where a significant proportion of missing data may lead to unreliable results. Conversely, all variables included in the multivariable logistic regression analysis of **Study III** were complete and thereby arterial lactate, an indicator of severe tissue hypoperfusion, was identified as a significant independent predictor of 90-day mortality.

5.4 STATISTICAL CONSIDERATIONS

5.4.1 Rational for use of logistic regression vs. Cox regression

Death at 90 days is a time-to-event outcome just as 30-day mortality is as for example a surgical quality metric used to assess surgical quality and to enable comparison of surgical performances between centers. However, this thesis focused on the binary outcome dead or alive at a fixed time point (90 days) without considering the time-to-event component, and not when in time the event (death) happened until the time point 90 days had been reached i.e. it was not in the interest of this thesis to consider if the individual patient had died on day one or day eighty-five, but only if the patient was dead at 90 days (90-day mortality). For this reason, logistic regression was used, which is in accordance to the most cited articles within the field, especially within the surgical domain.[2, 8, 44-49, 51, 53, 71, 80, 111] Furthermore, this facilitates comparison of data presented in **Study I-IV** with those seminal studies. Moreover, Cox regression relies on proportional hazards, which in the case of VA-ECMO patients is not fulfilled due to a much higher early than late mortality. Thus, logistic and not Cox regression was chosen through **Study I-IV**.

5.4.2 Collinearity

Looking at the initial model of **Study II** from a surgical point of view, it can be argued to keep AMI in the model as patients with AMI are empirically known to be associated with high risk of perioperative mortality and thereby being a factor always considered before accepting these patients for acute surgery. However, there was a lot of collinearity among variables which implied large overfitting and therefore impairing the predictive power of the model outside the sample analyzed. In fact, the high collinearity between AMI, CABG, and IHD, as they are likely to be the same thing (all patients receiving CABG obviously have IHD), in combination

with the limited number of events in **Study II** (too few survivors: AMI, n = 5; prior CABG, n = 2; prior PCI, n = 3; isolated CABG, n = 3 (**Table 7**) had to be addressed, in order to prevent that "insufficient" data would have resulted in an unstable multivariable model.[112] Furthermore, not all patients with IHD will be grafted unless presence of significant and graftable stenosis, whereby IHD has a higher prevalence than CABG and the removal of AMI further strengthens the classification of IHD. Thus, in order to improve the robustness of the model based on the arguments discussed, AMI and CABG were excluded from the final model. The same statistical considerations applied for pH and lactate, the latter being a more robust variable less sensitive to influence by $PaC0_2$ and administration of buffer solutions in the acute setting. Finally, 5 clinically meaningful and defined variables (IHD, age, arterial lactate, LVEF and MAP) were included in the multivariable logistic regression model.

Regarding further differentiation of surgical procedures in addition to the euroSCORE II classification (**Study II**), many, if not most, surgical procedures entail anything from minor perioperative corrections without reinstitution of CPB such as additional suturing of graft anastomoses due to local bleeding further on to major re-interventions such as switching from failed minimally invasive valve repair to open heart valve replacement. Even if unplanned procedures may have a negative impact on the cardiovascular state of individual patients leading to need for VA-ECMO support such further subdivision into non-validated procedural subgroups besides the validated euroSCORE II classification model will not improve identification of procedure related outcome predictors. Instead, it might complicate interpretation of data and impair comparison between centers especially when the numbers of included patients are limited, besides having a negative impact on power, multicollinearity and external validity (generalizability) of our findings. It was therefore chosen to keep the subdivision of surgical procedural subgroups in accordance to the euroSCORE II model in this thesis.

A further example of problematic collinearity addressed in the thesis concerns left and right ventricular deterioration. The vast majority of patients regardless of subgroup belonging, in addition to left ventricular deterioration, also had a significant right ventricular dysfunction. However, to determine if the right ventricular deterioration was of a primary, combined or secondary origin to left ventricular deterioration is challenging. Furthermore, in comparison to the relatively more precise echocardiographic quantification of left ventricular function, right ventricular deterioration was imprecisely characterized as being "significant" and thereby difficult to interpret. In addition, there was an extremely high correlation between "right

ventricular failure" and the LVEF in the multicollinearity analysis. Thus, we avoided introducing a right ventricular failure variable due to the above-mentioned reasons.

5.4.3 Confounders

With the aim to provide a model to predict outcome after VA-ECMO, potential confounders should be should be addressed. For example, in **Study II** it may be questioned when LVEF and MAP were registered, before surgery or just before VA-ECMO, in order to analyze these variables as pre-VA-ECMO variables, as it is well known that when the heart is on CPB LVEF is difficult to assess. The LVEF was recorded just before initiation (cannulation) of VA-ECMO and not before surgery (**Study II**). LVEF can be difficult to assess during CPB at full CPB flow rates. However, in patients who cannot be weaned from CPB, VA-ECMO will only be initiated after weaning attempts from CPB have failed. Intraoperative transesophageal echocardiography (TEE) is the routine method and main diagnostic tool to perioperatively evaluate the biventricular function (LVEF, valves etc.) before separating the patient from CPB. LVEF is assessed at the lowest possible CPB flow (weaning) rate thereby enhancing the accuracy in LVEF evaluation compared with if the assessment would be attempted during full CPB flow (which underestimates LVEF as indicated by the remark given). This method is not different from the well-established routine method in predicting the probability of successful weaning by assessing LVEF during lowest possible VA-ECMO flow rate when weaning and separation is attempted from VA-ECMO support to a mechanically unsupported heart. Replacing pre-VA-ECMO LVEF for preoperative (pre-CPB) LVEF would in most cases also overestimate the "factual" pre-VA-ECMO LVEF, the latter being the LVEF which the decision mainly is made to initiate VA-ECMO upon. It would also be challenging to discuss why the proportion of patients with normal and near normal pre-CPB LVEF were not able to be separated from CPB, when the decision was made to initiate VA-ECMO in the same patients de facto having a lower postoperative pre-VA-ECMO LVEF i.e. patients would be classified to have postcardiotomy cardiogenic shock but with (falsely) preserved or near normal LVEF. Moreover, using pre-VA-ECMO LVEF is a more consistent approach when comparing post CPB/pre-VA-ECMO characteristics of patients regardless if they were transitioned from CPB directly to VA-ECMO or later during the first postoperative hours or days. To compare pre-CPB LVEF in the patients cannulated in the OR with the pre-VA-ECMO LVEF in the patients cannulated later during the postoperative course would further complicate the assessment of pre-VA-ECMO LVEF as an outcome predictor as pre/post CPB LVEF is not the same variable in time. In summary, pre-CPB LVEF should not be used as a surrogate to pre-VA-ECMO LVEF as in the same way pre-VA-ECMO LVEF is not

considered when weaning from VA-ECMO is initiated if the aim is to assess the present LVEF influence on weaning success and outcome.

The MAP was in the same way measured just before initiation (cannulation) of VA-ECMO not before CPB as pre-CPB MAP does not reflect the pre-VA-ECMO MAP after several hours of surgery, aortic cross clamp, cardioplegia, or in the patients who were transferred to the ICU before VA-ECMO support was initiated.

It may be questioned why ECG as part of a cardiac evaluation just before VA-ECMO initiation was not included in the analysis in patients with refractory postcardiotomy cardiogenic shock. Systemic hypoperfusion caused by impaired myocardial contractility, is primarily verified by echocardiography (TTE/TEE) and hemodynamic monitoring, which are two of the clinical cornerstones included in the decision to initiate VA-ECMO support rather than ECG changes (**Study II**). In a minority of cases arrhythmias or electrocardiographic (ECG) ST-T changes can occur after cardioversion on CPB or during weaning from CPB, which depending on etiology in the majority of cases will respond either to or with a combination of pharmacology, cardioversion, pacemaker support, or in selected cases need for further reperfusion, valvular re-intervention or re-grafting of coronaries before final weaning from CPB or switch to VA-ECMO support is undertaken. The vast majority of these intraoperatively registered ECG changes of critical etiology will thereby have resolved before separation from CPB or switch to VA-ECMO. Post-CPB or pre-VA-ECMO ECG has therefore not routinely been documented to allow for inclusion or evaluation in this retrospective study.

5.5 CLINICAL IMPLICATIONS

This thesis identified in total four independent pre-implant predictors for 90-day mortality in patients with refractory cardiogenic shock or cardiac arrest prior to VA-ECMO initiation. The identified independent predictors for 90-day mortality after VA-ECMO initiation related to the different study populations (**Study I-IV**) are presented in **Table 16**. These predictors are easily obtainable for pre-VA-ECMO risk prediction and may help to use VA-ECMO more efficiently for refractory cardiogenic shock in the different patient cohorts studied.

TABLE 16. Patient populations and identified independent pre-implant predictors of 90-day mortality after VA-ECMO initiation related to the studies included in the thesis

Study	Patient population	Predictors of 90-day mortality
I	Unselected, refractory cardiogenic shock	• Arterial lactate • No. of inotropes and vasopressors • Ischemic heart disease
II	Refractory postcardiotomy cardiogenic shock	• Arterial lactate • Ischemic heart disease
III	Unselected non-surgical, refractory cardiogenic shock	• Arterial lactate • No. of inotropes and vasopressors
IV	Cardiac arrest and CPR duration ≥1 minute before VA-ECMO	• Initial non-shockable rhythm • Ischemic heart disease • Arterial lactate

CPR, cardiopulmonary resuscitation; *VA-ECMO,* venoarterial extracorporeal membrane oxygenation

It should be noted that arterial lactate was a predictor of 90-day mortality in all studies (**Study I-IV**).

In unselected patients with refractory cardiogenic shock (**Study I**), the arterial lactate level, the number of inotropes and vasopressors, and the presence of IHD were independent pre-VA-ECMO predictors of 90-day mortality after VA-ECMO initiation.

In **Study II** on patients with refractory postcardiotomy cardiogenic shock, arterial lactate level and IHD were independent pre-VA-ECMO predictors of 90-day mortality. Furthermore, **Study II** suggest that VA-ECMO should be considered before profound hyperlactatemia occurs, especially in patients with IHD. Importantly, our analysis further demonstrated that neither any of the four euroSCORE II cardiac surgical subgroups, cardioplegic route, aortic cross clamp and CPB time nor age or gender independently predicted 90-day mortality.

In patients with unselected non-surgical refractory cardiogenic shock (**Study III**) arterial lactate level and number of inotropes and vasopressors were found to be independent preimplant predictors of 90-day mortality after VA-ECMO initiation. These findings imply that when VA-ECMO is considered it should be implanted before profound hyperlactatemia occurs and the number of inotropic and vasopressor agents has increased. Furthermore, this also implies not to prioritize specific etiologies of cardiogenic shock when deciding which patients that may benefit from VA-ECMO, decisions that often have to be made swiftly within the limited time available to assess complete information of the patient's background.

Study IV on unselected patients with cardiac arrest of verified or presumed cardiac etiology and with low-flow duration down to 1 minute prior to VA-ECMO initiation identified non-

shockable rhythm, IHD, and arterial lactate as independent pre-implant predictors for 90-day mortality after VA-ECMO initiation, whereas age, low-flow duration and ROSC were not significant. These findings may facilitate rapid decision making in the extreme setting of cardiac arrest, irrespectively if patients are cannulated during CPR (ECPR) or due to refractory postarrest cardiogenic shock after ROSC. Furthermore, these findings imply that primarily initial cardiac arrest rhythm followed by metabolic assessment, i.e. arterial lactate level and/or presence of IHD are more important than strict age or time limits when VA-ECMO is contemplated during CPR or in refractory postarrest cardiogenic shock.

5.6 LIMITATIONS

Some important limitations of the studies included in this thesis need to be mentioned. **Study I-IV** were based on retrospective observational data from a heterogeneous patient cohort with refractory cardiogenic shock and/or cardiac arrest followed by VA-ECMO and neither included matched control cohorts nor allowed for randomization. Nevertheless, the heterogeneity of patients with refractory cardiogenic shock and/or cardiac arrest reflects the clinical reality in tertiary centers offering VA-ECMO and therefore provides generalizability (external validity) of the findings. Furthermore, as data are observational, they are prone to selection bias and the limited sample sizes are too small to draw definitive recommendations.

The limited sample sizes in this thesis cannot rule out the risk of Type II errors, exemplified by the variable age. In Study I-IV age did not reach significance in contrast to several studies within the field.[2, 8, 32, 34, 40, 44-47, 49, 55, 111] However, this likely suggest that in previous less adjusted analyses age was important, whereas in our analysis, age was neutralized by the many other covariates in our study models. For example, age was associated with mortality in previous circulatory arrest studies related to VA-ECMO.[104, 105, 113] However, in studies that included lactate age did not reach statistical significance.[82, 83, 85, 86]

6 CONCLUSIONS

The specific conclusions were:

- In unselected patients with refractory cardiogenic shock, the arterial lactate level, the number of inotropes and vasopressors, and the presence of IHD were identified as independent pre-implant predictors of 90-day mortality after VA-ECMO initiation.

- In patients with refractory postcardiotomy cardiogenic shock, arterial lactate level and presence of IHD were identified as independent pre-implant predictors of 90-day mortality after VA-ECMO initiation.

- In an unselected non-surgical population with refractory cardiogenic shock arterial lactate level and number of inotropes and vasopressors were identified as independent pre-implant predictors of 90-day mortality after VA-ECMO initiation.

- In patients with cardiac arrest and CPR ≥1 minute before VA-ECMO initiation, non-shockable rhythm, IHD, and arterial lactate were identified as independent pre-implant predictors of 90-day mortality after VA-ECMO initiation, whereas low-flow duration, ROSC and age were not significant.

7 ACKNOWLEDGEMENTS

I would like to acknowledge

Jan van der Linden, main supervisor and Professor of Cardiothoracic Anesthesiology and Intensive Care, for his inspiration not only in research but also in clinical medicine. With the help of his vast scientific knowledge and support he has helped me tackle difficult methodological obstacles and guided me through this work. Without his untiring support this dissertation would never have seen the light of day.

Lars H. Lund, co-supervisor and Professor of Cardiology, initiated this line of research and shared his exemplary scientific knowledge during the development of this thesis.

Matthias Corbascio, co-supervisor and Associate Professor of Cardiothoracic Surgery, has provided surgical insights and continuous scientific analysis in the development of this thesis. He has been a great friend through tough times.

Manne Holm, M.D., Ph.D., has provided critical insights and support in the development of this thesis and is great research companion and co-author to discuss and dissect one's ideas.

Anders Franco-Cereceda, Professor of Cardiothoracic Surgery and Head of the Department of Molecular Medicine and Surgery, has been throughout this work a constant source of emotional and scientific support when none was required of him.

Ulrik Sartipy, Associate Professor of Cardiothoracic Surgery, is an absolute master of statistical analysis and I am grateful for all his assistance in navigating those waters.

All my colleagues at the Divisions of Cardiothoracic Anesthesiology and Intensive Care, Cardiothoracic Surgery and the ECMO center of Karolinska University Hospital who have supported me all these years.

My family and friends for their love and patience.

8 REFERENCES

1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med.* 1999;341:625-634.

2. Doll N, Kiaii B, Borger M, et al. Five-year results of 219 consecutive patients treated with extracorporeal membrane oxygenation for refractory postoperative cardiogenic shock. *Ann Thorac Surg.* 2004;77:151-157; discussion 157.

3. Reyentovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. *Nat Rev Cardiol.* 2016;13:481-492.

4. Westaby S, Kharbanda R, Banning AP. Cardiogenic shock in ACS. Part 1: prediction, presentation and medical therapy. *Nat Rev Cardiol.* 2011;9:158-171.

5. Westaby S, Anastasiadis K, Wieselthaler GM. Cardiogenic shock in ACS. Part 2: Role of mechanical circulatory support. *Nat Rev Cardiol.* 2012;9:195-208.

6. Abrams D, Combes A, Brodie D. Extracorporeal membrane oxygenation in cardiopulmonary disease in adults. *J Am Coll Cardiol.* 2014;63:2769-2778.

7. Xie A, Phan K, Tsai YC, Yan TD, Forrest P. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: a meta-analysis. *J Cardiothorac Vasc Anesth.* 2015;29:637-645.

8. Slottosch I, Liakopoulos O, Kuhn E, et al. Outcomes after peripheral extracorporeal membrane oxygenation therapy for postcardiotomy cardiogenic shock: a single-center experience. *J Surg Res.* 2013;181:e47-55.

9. de Chambrun MP, Brechot N, Lebreton G, et al. Venoarterial extracorporeal membrane oxygenation for refractory cardiogenic shock post-cardiac arrest. *Intensive Care Med.* 2016;42:1999-2007.

10. Lim HS, Howell N, Ranasinghe A. Extracorporeal Life Support: Physiological Concepts and Clinical Outcomes. *J Card Fail.* 2017;23:181-196.

11. Black MC, Slaughter MS. Proactive or reactive? Best approach to limb ischemia in peripheral venoarterial extracorporeal life support. *J Thorac Cardiovasc Surg.* 2016;151:1745-1746.

12. Schmidt M, Pellegrino V, Combes A, Scheinkestel C, Cooper DJ, Hodgson C. Mechanical ventilation during extracorporeal membrane oxygenation. *Crit Care.* 2014;18:203.

13. Napp LC, Kuhn C, Hoeper MM, et al. Cannulation strategies for percutaneous extracorporeal membrane oxygenation in adults. *Clin Res Cardiol.* 2016;105:283-296.

14. Schmidt M, Burrell A, Roberts L, et al. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J.* 2015;36:2246-2256.

15. Paden ML, Rycus PT, Thiagarajan RR. Update and outcomes in extracorporeal life support. *Semin Perinatol.* 2014;38:65-70.

16. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *Jama.* 1979;242:2193-2196.

17. Hill JD, O'Brien TG, Murray JJ, et al. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. *N Engl J Med.* 1972;286:629-634.

18. Ouweneel DM, Henriques JP. Percutaneous cardiac support devices for cardiogenic shock: current indications and recommendations. *Heart.* 2012;98:1246-1254.

19. Werdan K, Gielen S, Ebelt H, Hochman JS. Mechanical circulatory support in cardiogenic shock. *Eur Heart J.* 2014;35:156-167.

20. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. *Eur Heart J.* 2015;36:1223-1230.

21. Lee JM, Park J, Kang J, et al. The efficacy and safety of mechanical hemodynamic support in patients undergoing high-risk percutaneous coronary intervention with or without cardiogenic shock: Bayesian approach network meta-analysis of 13 randomized controlled trials. *Int J Cardiol.* 2015;184:36-46.

22. Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. *Ann Thorac Surg.* 2014;97:610-616.

23. Meani P, Pappalardo F. The step forward for VA ECMO: left ventricular unloading! *J Thorac Dis.* Vol 9. China2017:4149-4151.

24. Napp LC, Kuhn C, Bauersachs J. ECMO in cardiac arrest and cardiogenic shock. *Herz.* 2017.

25. Kitamura M, Shibuya M, Kurihara H, Akimoto T, Endo M, Koyanagi H. Effective cross-circulation technique of venoarterial bypass for differential hypoxia condition. *Artif Organs.* 1997;21:786-788.

26. Choi JH, Kim SW, Kim YU, et al. Application of veno-arterial-venous extracorporeal membrane oxygenation in differential hypoxia. *Multidiscip Respir Med.* 2014;9:55.

27. Geyer M, Gohrbandt B, Sagoschen I, et al. Pitfalls of cannulation for extracorporeal life support: review of the literature and illustrative case presentation. *J Artif Organs.* 2018;21:8-16.

28. Sheu JJ, Tsai TH, Lee FY, et al. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. *Crit Care Med.* 2010;38:1810-1817.

29. Combes A, Leprince P, Luyt CE, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. *Crit Care Med.* 2008;36:1404-1411.

30. Belle L, Mangin L, Bonnet H, et al. Emergency extracorporeal membrane oxygenation in a hospital without on-site cardiac surgical facilities. *EuroIntervention.* 2012;8:375-382.

31. Beurtheret S, Mordant P, Paoletti X, et al. Emergency circulatory support in refractory cardiogenic shock patients in remote institutions: a pilot study (the cardiac-RESCUE program). *Eur Heart J.* 2013;34:112-120.

32. de Waha S, Fuernau G, Desch S, et al. Long-term prognosis after extracorporeal life support in refractory cardiogenic shock: results from a real-world cohort. *EuroIntervention.* 2016;11:1363-1371.

33. Sakamoto S, Taniguchi N, Nakajima S, Takahashi A. Extracorporeal life support for cardiogenic shock or cardiac arrest due to acute coronary syndrome. *Ann Thorac Surg.* 2012;94:1-7.

34. Guihaire J, Dang Van S, Rouze S, et al. Clinical outcomes in patients after extracorporeal membrane oxygenation support for post-cardiotomy cardiogenic shock: a single-centre experience of 92 casesdagger. *Interact Cardiovasc Thorac Surg.* 2017.

35. Kuroki N, Abe D, Iwama T, et al. Prognostic effect of estimated glomerular filtration rate in patients with cardiogenic shock or cardiac arrest undergoing percutaneous veno-arterial extracorporeal membrane oxygenation. *J Cardiol.* 2016;68:439-446.

36. Paden ML, Conrad SA, Rycus PT, Thiagarajan RR. Extracorporeal Life Support Organization Registry Report 2012. *Asaio j.* 2013;59:202-210.

37. Thiagarajan RR, Barbaro RP, Rycus PT, et al. Extracorporeal Life Support Organization Registry International Report 2016. *Asaio j.* 2017;63:60-67.

38. Huesch M, Brehm C. The Challenges in Predicting ECMO Survival, and a Path Forward. *Asaio j.* 2017;63:847-848.

39. Truby L, Mundy L, Kalesan B, et al. Contemporary Outcomes of Venoarterial Extracorporeal Membrane Oxygenation for Refractory Cardiogenic Shock at a Large Tertiary Care Center. *Asaio j.* 2015;61:403-409.

40. Muller G, Flecher E, Lebreton G, et al. The ENCOURAGE mortality risk score and analysis of long-term outcomes after VA-ECMO for acute myocardial infarction with cardiogenic shock. *Intensive Care Med.* 2016;42:370-378.

41. Tsai TY, Tsai FC, Fan PC, et al. Application of the Age, Creatinine, and Left Ventricular Ejection Fraction Score for Patients on Extracorporeal Membrane Oxygenation. *Artif Organs.* 2016.

42. Demondion P, Fournel L, Golmard JL, Niculescu M, Pavie A, Leprince P. Predictors of 30-day mortality and outcome in cases of myocardial infarction with cardiogenic shock treated by extracorporeal life support. *Eur J Cardiothorac Surg.* 2014;45:47-54.

43. Burrell AJ, Pellegrino VA, Wolfe R, et al. Long-term survival of adults with cardiogenic shock after venoarterial extracorporeal membrane oxygenation. *J Crit Care.* 2015;30:949-956.

44. Rastan AJ, Dege A, Mohr M, et al. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. *J Thorac Cardiovasc Surg.* 2010;139:302-311, 311.e301.

45. Papadopoulos N, Marinos S, El-Sayed Ahmad A, et al. Risk factors associated with adverse outcome following extracorporeal life support: analysis from 360 consecutive patients. *Perfusion.* 2015;30:284-290.

46. Park SJ, Kim JB, Jung SH, Choo SJ, Chung CH, Lee JW. Outcomes of extracorporeal life support for low cardiac output syndrome after major cardiac surgery. *J Thorac Cardiovasc Surg.* 2014;147:283-289.

47. Elsharkawy HA, Li L, Esa WA, Sessler DI, Bashour CA. Outcome in patients who require venoarterial extracorporeal membrane oxygenation support after cardiac surgery. *J Cardiothorac Vasc Anesth.* 2010;24:946-951.

48. Hsu PS, Chen JL, Hong GJ, et al. Extracorporeal membrane oxygenation for refractory cardiogenic shock after cardiac surgery: predictors of early mortality and outcome from 51 adult patients. *Eur J Cardiothorac Surg.* 2010;37:328-333.

49. Li CL, Wang H, Jia M, Ma N, Meng X, Hou XT. The early dynamic behavior of lactate is linked to mortality in postcardiotomy patients with extracorporeal membrane oxygenation support: A retrospective observational study. *J Thorac Cardiovasc Surg.* 2015;149:1445-1450.

50. Chen SW, Tsai FC, Lin YS, et al. Long-term outcomes of extracorporeal membrane oxygenation support for postcardiotomy shock. *J Thorac Cardiovasc Surg.* 2017;154:469-477.e462.

51. Bakhtiary F, Keller H, Dogan S, et al. Venoarterial extracorporeal membrane oxygenation for treatment of cardiogenic shock: clinical experiences in 45 adult patients. *J Thorac Cardiovasc Surg.* 2008;135:382-388.

52. Fukuhara S, Takeda K, Garan AR, et al. Contemporary mechanical circulatory support therapy for postcardiotomy shock. *Gen Thorac Cardiovasc Surg.* 2016;64:183-191.

53. Loforte A, Marinelli G, Musumeci F, et al. Extracorporeal membrane oxygenation support in refractory cardiogenic shock: treatment strategies and analysis of risk factors. *Artif Organs.* 2014;38:E129-141.

54. Whitman GJ. Extracorporeal membrane oxygenation for the treatment of postcardiotomy shock. *J Thorac Cardiovasc Surg.* 2017;153:95-101.

55. Fiser SM, Tribble CG, Kaza AK, et al. When to discontinue extracorporeal membrane oxygenation for postcardiotomy support. *Ann Thorac Surg.* 2001;71:210-214.

56. Squiers JJ, Lima B, DiMaio JM. Contemporary extracorporeal membrane oxygenation therapy in adults: Fundamental principles and systematic review of the evidence. *J Thorac Cardiovasc Surg.* 2016;152:20-32.

57. Davierwala PM, Leontyev S, Verevkin A, et al. Temporal Trends in Predictors of Early and Late Mortality After Emergency Coronary Artery Bypass Grafting for Cardiogenic Shock Complicating Acute Myocardial Infarction. *Circulation.* 2016;134:1224-1237.

58. Sawamura A, Okumura T, Hirakawa A, et al. Early Prediction Model for Successful Bridge to Recovery in Patients With Fulminant Myocarditis Supported With Percutaneous Venoarterial Extracorporeal Membrane Oxygenation- Insights From the CHANGE PUMP Study. *Circ J.* 2018;82:699-707.

59. Pozzi M, Banfi C, Grinberg D, et al. Veno-arterial extracorporeal membrane oxygenation for cardiogenic shock due to myocarditis in adult patients. *J Thorac Dis.* 2016;8:E495-502.

60. Mirabel M, Luyt CE, Leprince P, et al. Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support. *Crit Care Med.* 2011;39:1029-1035.

61. Dangers L, Brechot N, Schmidt M, et al. Extracorporeal Membrane Oxygenation for Acute Decompensated Heart Failure. *Crit Care Med.* 2017;45:1359-1366.

62. Cheng A, Sun HY, Tsai MS, et al. Predictors of survival in adults undergoing extracorporeal membrane oxygenation with severe infections. *J Thorac Cardiovasc Surg.* 2016;152:1526-1536.e1521.

63. Fux T, Holm M, Corbascio M, van der Linden J, Lund LH. Pre-Implant Outcome Predictors in Patients With Refractory Cardiogenic Shock Supported With VA-ECMO. *J Am Coll Cardiol.* 2017;70:2094-2096.

64. Peigh G, Cavarocchi N, Keith SW, Hirose H. Simple new risk score model for adult cardiac extracorporeal membrane oxygenation: simple cardiac ECMO score. *J Surg Res.* 2015;198:273-279.

65. Wu MY, Lee MY, Lin CC, Chang YS, Tsai FC, Lin PJ. Resuscitation of non-postcardiotomy cardiogenic shock or cardiac arrest with extracorporeal life support: the role of bridging to intervention. *Resuscitation.* 2012;83:976-981.

66. Tarzia V, Bortolussi G, Bianco R, et al. Extracorporeal life support in cardiogenic shock: Impact of acute versus chronic etiology on outcome. *J Thorac Cardiovasc Surg.* 2015;150:333-340.

67. Chen WC, Huang KY, Yao CW, et al. The modified SAVE score: predicting survival using urgent veno-arterial extracorporeal membrane oxygenation within 24 hours of arrival at the emergency department. *Crit Care.* 2016;20:336.

68. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis.* 2014;63:713-735.

69. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation.* 2004;110:3385-3397.

70. Khosravani H, Shahpori R, Stelfox HT, Kirkpatrick AW, Laupland KB. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. *Crit Care.* 2009;13:R90.

71. Park SJ, Kim SP, Kim JB, et al. Blood lactate level during extracorporeal life support as a surrogate marker for survival. *J Thorac Cardiovasc Surg.* 2014;148:714-720.

72. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation.* 1970;41:989-1001.

73. Vincent JL, De Backer D. Circulatory shock. *N Engl J Med.* 2013;369:1726-1734.

74. Fall PJ, Szerlip HM. Lactic acidosis: from sour milk to septic shock. *J Intensive Care Med.* 2005;20:255-271.

75. Fuller BM, Dellinger RP. Lactate as a hemodynamic marker in the critically ill. *Curr Opin Crit Care.* 2012;18:267-272.

76. Haanschoten MC, Kreeftenberg HG, Arthur Bouwman R, van Straten AH, Buhre WF, Soliman Hamad MA. Use of Postoperative Peak Arterial Lactate Level to Predict Outcome After Cardiac Surgery. *J Cardiothorac Vasc Anesth.* 2017;31:45-53.

77. Minton J, Sidebotham DA. Hyperlactatemia and Cardiac Surgery. *J Extra Corpor Technol.* 2017;49:7-15.

78. Lopez-Delgado JC, Esteve F, Javierre C, et al. Evaluation of Serial Arterial Lactate Levels as a Predictor of Hospital and Long-Term Mortality in Patients After Cardiac Surgery. *J Cardiothorac Vasc Anesth.* 2015;29:1441-1453.

79. Vincent JL, Quintairos ESA, Couto L, Jr., Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. *Crit Care.* 2016;20:257.

80. Hajjar LA, Almeida JP, Fukushima JT, et al. High lactate levels are predictors of major complications after cardiac surgery. *J Thorac Cardiovasc Surg.* 2013;146:455-460.

81. Flecher E, Anselmi A, Corbineau H, et al. Current aspects of extracorporeal membrane oxygenation in a tertiary referral centre: determinants of survival at follow-up. *Eur J Cardiothorac Surg.* 2014;46:665-671; discussion 671.

82. Ellouze O, Vuillet M, Perrot J, et al. Comparable Outcome of Out-of-Hospital Cardiac Arrest and In-Hospital Cardiac Arrest Treated With Extracorporeal Life Support. *Artif Organs.* 2018;42:15-21.

83. Zhang Y, Li CS, Yuan XL, et al. Association of serum biomarkers with outcomes of cardiac arrest patients undergoing ECMO. *Am J Emerg Med.* 2018.

84. Debaty G, Babaz V, Durand M, et al. Prognostic factors for extracorporeal cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac arrest. A systematic review and meta-analysis. *Resuscitation.* 2017;112:1-10.

85. Dennis M, McCanny P, D'Souza M, et al. Extracorporeal cardiopulmonary resuscitation for refractory cardiac arrest: A multicentre experience. *Int J Cardiol.* 2017;231:131-136.

86. Jung C, Janssen K, Kaluza M, et al. Outcome predictors in cardiopulmonary resuscitation facilitated by extracorporeal membrane oxygenation. *Clin Res Cardiol.* 2016;105:196-205.

87. Donnino MW, Andersen LW, Giberson T, et al. Initial lactate and lactate change in post-cardiac arrest: a multicenter validation study. *Crit Care Med.* 2014;42:1804-1811.

88. Jentzer JC, Chonde MD, Dezfulian C. Myocardial Dysfunction and Shock after Cardiac Arrest. *Biomed Res Int.* 2015;2015:314796.

89. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Ischemia/Reperfusion. *Compr Physiol.* 2016;7:113-170.

90. Wang CH, Huang CH, Chang WT, et al. Monitoring of serum lactate level during cardiopulmonary resuscitation in adult in-hospital cardiac arrest. *Crit Care.* 2015;19:344.

91. Megarbane B, Deye N, Aout M, et al. Usefulness of routine laboratory parameters in the decision to treat refractory cardiac arrest with extracorporeal life support. *Resuscitation.* 2011;82:1154-1161.

92. Megarbane B, Leprince P, Deye N, et al. Emergency feasibility in medical intensive care unit of extracorporeal life support for refractory cardiac arrest. *Intensive Care Med.* 2007;33:758-764.

93. Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med.* 2011;183:847-855.

94. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med.* 2010;11:234-238.

95. Katz JN, Stebbins AL, Alexander JH, et al. Predictors of 30-day mortality in patients with refractory cardiogenic shock following acute myocardial infarction despite a patent infarct artery. *Am Heart J.* 2009;158:680-687.

96. Barge-Caballero E, Segovia-Cubero J, Gonzalez-Vilchez F, et al. Evaluation of the preoperative vasoactive-inotropic score as a predictor of postoperative outcomes in patients undergoing heart transplantation. *Int J Cardiol.* 2015;185:192-194.

97. Kormos RL, Gasior TA, Kawai A, et al. Transplant candidate's clinical status rather than right ventricular function defines need for univentricular versus biventricular support. *J Thorac Cardiovasc Surg.* 1996;111:773-782; discussion 782-773.

98. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. *Int J Cardiol.* 2013;168:934-945.

99. Sleeper LA, Reynolds HR, White HD, Webb JG, Dzavik V, Hochman JS. A severity scoring system for risk assessment of patients with cardiogenic shock: a report from the SHOCK Trial and Registry. *Am Heart J.* 2010;160:443-450.

100. El-Sherif N, Boutjdir M, Turitto G. Sudden Cardiac Death in Ischemic Heart Disease: Pathophysiology and Risk Stratification. *Card Electrophysiol Clin.* 2017;9:681-691.

101. Cesana F, Avalli L, Garatti L, et al. Effects of extracorporeal cardiopulmonary resuscitation on neurological and cardiac outcome after ischaemic refractory cardiac arrest. *Eur Heart J Acute Cardiovasc Care.* 2017:2048872617737041.

102. Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet.* 2008;372:554-561.

103. Kagawa E, Inoue I, Kawagoe T, et al. Assessment of outcomes and differences between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal life support. *Resuscitation.* 2010;81:968-973.

104. Park SB, Yang JH, Park TK, et al. Developing a risk prediction model for survival to discharge in cardiac arrest patients who undergo extracorporeal membrane oxygenation. *Int J Cardiol.* 2014;177:1031-1035.

105. Wang CH, Chou NK, Becker LB, et al. Improved outcome of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest--a comparison with that for extracorporeal rescue for in-hospital cardiac arrest. *Resuscitation.* 2014;85:1219-1224.

106. Yukawa T, Kashiura M, Sugiyama K, Tanabe T, Hamabe Y. Neurological outcomes and duration from cardiac arrest to the initiation of extracorporeal membrane oxygenation in patients with out-of-hospital cardiac arrest: a retrospective study. *Scand J Trauma Resusc Emerg Med.* 2017;25:95.

107. Chen CT, Chiu PC, Tang CY, et al. Prognostic factors for survival outcome after in-hospital cardiac arrest: An observational study of the oriental population in Taiwan. *J Chin Med Assoc.* 2016;79:11-16.

108. Wengenmayer T, Rombach S, Ramshorn F, et al. Influence of low-flow time on survival after extracorporeal cardiopulmonary resuscitation (eCPR). *Crit Care.* 2017;21:157.

109. Smedira NG, Moazami N, Golding CM, et al. Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: survival at five years. *J Thorac Cardiovasc Surg.* 2001;122:92-102.

110. Carroll BJ, Shah RV, Murthy V, et al. Clinical Features and outcomes in adults with cardiogenic shock supported by extracorporeal membrane oxygenation. *Am J Cardiol.* 2015;116:1624-1630.

111. Wu MY, Lin PJ, Lee MY, et al. Using extracorporeal life support to resuscitate adult postcardiotomy cardiogenic shock: treatment strategies and predictors of short-term and midterm survival. *Resuscitation.* 2010;81:1111-1116.

112. Blackstone EH. Sufficient data. *J Thorac Cardiovasc Surg.* 2016;152:1235-1236.

113. Richardson AS, Schmidt M, Bailey M, Pellegrino VA, Rycus PT, Pilcher DV. ECMO Cardio-Pulmonary Resuscitation (ECPR), trends in survival from an international multicentre cohort study over 12-years. *Resuscitation.* 2017;112:34-40.